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Vol. 227, No. 6 JUNE, 1954 No. 986

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JUNE, 1954

ORIGINAL ARTICLES

SHOULDER DYSFUNCTION IN PULMONARY TUBERCULOSIS

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It is commonly known that any condition which necessitates prolonged immobilization of the shoulder and arm is frequently accompanied by pain and stiffness of the shoulder. Ghormley[3] has pointed out that frozen shoulder "is often found as a complication in any condition requiring prolonged fixation of the shoulder joint." Neviaser[6] has emphasized that disuse and inactivity are the common denominator and play an important role in the etiology of frozen shoulder. Lippmann[4] and DePalma[2] have stated that frozen shoulder occurs frequently in patients with pulmonary disease. However, there has been only one report devoted to the problem of shoulder pain in pulmonary tuberculosis[7].

In the usual case, the first symptoms of shoulder dysfunction are pain and stiffness in the shoulder or upper arm. The pain is aggravated by active movement of the arm, and sleep is frequently interrupted by it. Most patients with a painful shoulder gradually recover spontaneously. A small number remains with a chronically painful shoulder or goes on to develop limitation of motion of the glenohumeral joint. This may be mild or may progress to the point where motion of the arm is almost entirely due to scapular rotation and elevation of the shoulder. After a period of months or years, many of the severely affected patients recover spontaneously. Pain gradually diminishes, and the patient regains use of the extremity. The disability commonly lasts from 3 months to 2 years, and most patients recover in 9 or 10 months[1]. The course is not always benign, however, and a permanently stiff shoulder may remain[8].

Among the patients referred to the Physical Medicine Service at the Fitzsimons Army Hospital because of pain and stiffness of the shoulder, it was noted that many were hospitalized primarily for the treatment of pulmonary tuberculosis. A study was therefore

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undertaken to determine the frequency of shoulder disorders in patients hospitalized for pulmonary tuberculosis, and to attempt to evaluate factors responsible for their development.

Methods. In order to determine the frequency of shoulder dysfunction in patients hospitalized for the treatment of pulmonary tuberculosis, and to evaluate factors influencing its development, all patients hospitalized on three randomly selected wards devoted to the treatment of tuberculosis at the Fitzsimons Army Hospital were carefully questioned concerning pain, stiffness, and limitation of movement of their shoulders. The shoulders of each patient were carefully examined by inspection and palpation at rest and during abduction, adduction, rotation, flexion and extension of the arms. In addition to the data on the shoulder, the following information was obtained by questioning and from the clinical records of each patient: age; race; sex; duration, type, severity, and location of tuberculosis; duration of bed rest; the type of treatment; past history of shoulder dysfunction, and complicating illnesses.

Patients who had undergone any thoracic surgical procedure or who had any condition such as arthritis or injuries of the upper extremities which might predispose them to develop shoulder dysfunction were excluded from this study. This initial phase of the survey yielded 199 acceptable patients with pulmonary tuberculosis. When it was noted that severe shoulder disability was rare in patients under the age of forty, the study was extended to include almost all the patients over 40 years of age hospitalized for the treatment of pulmonary tuberculosis, who had not undergone any thoracic surgical procedure and who were free of other predisposing conditions. Sixty-one additional patients between the ages of 40 and 82 years were included, resulting in a total of 260 patients. Since the findings in this selected group corresponded very closely to those in the randomly chosen series, the two have been combined in studying factors influencing the development and course of shoulder disability.

The exact pathologic process causing shoulder dysfunction is difficult to evaluate clinically. Several have been described, but they can be confirmed only at operation or by postmortem examination. We have therefore classified these patients by the severity of their disability, rather than the exact etiologic factors. Grade O signifies no shoulder disability. Grade I means pain and subjective complaints of stiffness, but no objective change in the range of motion of the shoulder. Grade II signifies the ability to abduct the arm more than 90 degrees but less than 180 degrees, and Grade III denotes inability to abduct the arm more than 90 degrees.

Results. 1. THE EFFECT OF AGE ON THE DEVELOPMENT OF SHOULDER DISABILITY (FIG. 1). Of 136 patients under 40 years of age, 85.2% had no shoulder complaints, 13.2% had pain and stiffness only (Grade I disability), and only 1.6% had some limitation of motion (Grade II disability). Among 124 patients over the age of 40 years, only 58.9% had no shoulder complaints, 16.9% suffered with pain and stiffness (Grade I disability), while 24.2% had definite limitation of motion of the shoulder joint (Grade II and III disability). The difference between the two groups was found to be statistically significant, with p for chi square less than .0001.

The mean age of all the patients studied was 40.4 years. That of patients without shoulder dysfunction was 38.3 years, while that of patients with Grade I disability was 43.7 years and of patients with Grade II and III dysfunction was 51.7 years. The difference between the mean ages of the whole group and of patients without or with only mild shoulder disability was statistically not significant. The difference between the mean ages of the whole group and of patients with Grade II and III dysfunction was 5.6 times its standard error, which is statistically significant.

2. THE EFFECT OF DURATION AND COMPLETENESS OF BED REST ON THE DEVELOPMENT OF SHOULDER DYSFUNCTION (FIG. 2). All patients with shoulder complaints developed their first symptoms while they were at complete or almost complete bed rest. Whereas, many of these patients continued to have

shoulder dysfunction after their activities had been increased, none developed his initial symptoms at a time when his rest regimen had been liberalized. Among the patients with shoulder dysfunction, 84.5% developed symptoms within 6 months of their confinement to bed, 8.5% between 7 and 12 months, and only 7.0% were in bed more than one year prior to the development of shoulder disability.

3. THE EFFECT OF THE DURATION OF TUBERCULOSIS ON THE DEVELOPMENT OF SHOULDER DYSFUNCTION (TABLE 1). There was no apparent correlation between the duration of tuberculosis and the development of shoulder complaints. Among the patients without shoulder complaints, 68.3% had tuberculosis less than 2 years, and 31.7% more than 2 years. In the group with shoulder disability 64.4% had pulmonary tuberculosis less than 2 years, and 35.6% longer than 2 years. The difference between the two groups was found to be statistically not significant, with p for chi-square more than 0.5.

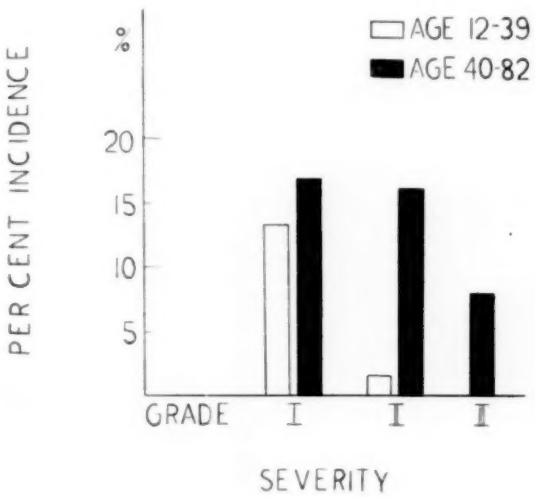

Fig. 1—The effect of age on the development of shoulder disability.

TABLE 1.—THE EFFECT OF THE DURATION OF TUBERCULOSIS ON THE DEVELOPMENT OF SHOULDER DYSFUNCTION

Type of Patient	*Total Number*	*Duration of Pulmonary Tuberculosis*	
		Less Than 2 Years	*More Than 2 Years*
Patients without shoulder disability	189	68.3%	31.7%
Patients with shoulder disability	71	64.4%	35.6%

4. THE EFFECT OF SEX ON THE DEVELOPMENT OF SHOULDER DYSFUNCTION (TABLE 2). Of the patients without shoulder dysfunction, 21.2% were women, and 78.8% were men. Of the group with shoulder complaints, only 9.9% were female, and 90.1% were male. No statement regarding the relative incidence of shoulder disability in the

two sexes can be made because at the time of this study there were only 4 women as compared to 120 men over the age of 40 on the wards that were included in this survey. As previously stated, this is the group that is most commonly affected by shoulder disorders.

5. THE EFFECT OF RACE ON THE DEVELOPMENT OF SHOULDER DYSFUNCTION (TABLE 3). There was no significant difference in the frequency of shoulder disorders in white and Negro patients. Of the patients without shoulder complaints 77.2% were white, and 20.6% were Negro. Among the patients with symptoms referable to the shoulder, 84.5% were white and 15.5% were Negro. The difference between the two groups was found to be statistically not significant, with p for chi-square more than 0.3.

6. THE EFFECT OF THE MODE OF TREATMENT OF TUBERCULOSIS ON THE DEVELOPMENT OF SHOULDER DYSFUNCTION (TABLE 4). None of the medical measures commonly used in the treatment of tuberculosis had any significant effect on the development of shoulder complaints. Of the patients with no symptoms referable to the shoulder, 27% received pneumoperitoneum, while 29.6% of those with shoulder complaints were subjected to pneumoperitoneum. Of the patients without shoulder dysfunction 92.1% received streptomycin and either PAS (paraaminosalicylic acid) or isoniazid; 19.3% of them received the injection in the arm. Of the patients with shoulder disorders, 98.6% received streptomycin and one of the other drugs, and 14.1% of them received the injections in the arm. The differences between the two groups were found to be statistically not significant using the chi-square method.

7. THE EFFECT OF THE LOCATION OF TUBERCULOSIS ON THE DEVELOPMENT OF SHOULDER DYSFUNCTION. There was no

TABLE 2.—THE EFFECT OF SEX ON THE DEVELOPMENT OF SHOULDER DYSFUNCTION

Type of Patient	*Total Number*	*Sex*	
		Male	*Female*
Patients without shoulder disability	189	78.8%	21.2%
Patients with shoulder disability	71	90.1%	9.9%

TABLE 3.—THE EFFECT OF RACE ON THE DEVELOPMENT OF SHOULDER DYSFUNCTION

Type of Patient	*Total Number*	*Race*		
		White	*Negro*	*Other*
Patients without shoulder disability	189	77.2%	20.6%	2.2%
Patients with shoulder disability	71	84.5%	15.5%	—

TABLE 4.—THE EFFECT OF THE MODE OF TREATMENT OF TUBERCULOSIS ON THE DEVELOPMENT OF SHOULDER DYSFUNCTION

Type of Patient	*Total Number*	*Mode of Treatment*		
		Pneumoperitoneum	*Streptomycin*	*Streptomycin in the Arm*
Patients without shoulder disability	189	27.0%	92.1%	19.3%
Patients with shoulder disability	71	29.6%	98.6%	14.1%

obvious relationship between the location of the tuberculous process in the lungs and the shoulder disability. Many patients had bilateral shoulder dysfunction, but frequently only unilateral pulmonary disease. In some with unilateral shoulder pain the tuberculous process was in the opposite lung. Shoulder disability was present in patients with tuberculosis involving either the apical or the diaphragmatic portions of the lung, and in those with pleural involvement, as well as those without it.

8. THE COURSE OF THE SHOULDER DISABILITY AND ITS TREATMENT. A few of the patients, usually those most severely incapacitated by the shoulder lesion, received therapy to relieve the shoulder dysfunction. Treatment consisted of analgesics and an active program of shoulder exercises supplemented by heat and massage. Only a small number of the patients so treated noted significant improvement.

Of the patients who received no physical therapy, spontaneous improvement or disappearance of symptoms occurred in a few. The improvement frequently coincided with an increase in the patients' activities, and was most common in patients with Grade I disability. One patient with Grade II, and 3 patients with Grade III dysfunction experienced spontaneous cures. One patient is of special interest since he developed Grade III dysfunction of his right shoulder during his first hospital admission. This disappeared completely 2 months after he left the hospital against advice to resume his previous occupation, only to recur in both shoulders one month after his return to the hospital and almost complete bed rest 6 months later.

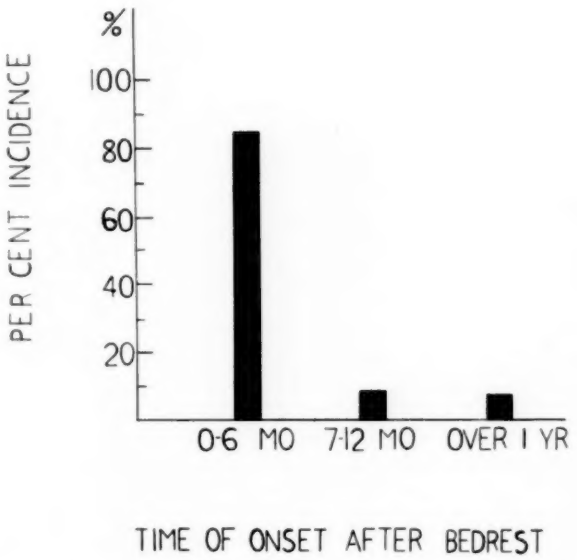

Fig. 2.—The effect of duration and completeness of bed rest on the development of shoulder dysfunction.

Discussion and Conclusions. Most reviews dealing with the problem of the frozen shoulder mention the frequency of its occurrence in patients with pulmonary diseases[2-4]. However,

to the best of our knowledge, only one study[7] has been published devoted to this problem in relation to pulmonary tuberculosis, and this author does not attempt to determine the frequency of this complication, nor does he offer any plan for its prevention or treatment. This survey was therefore undertaken to determine the frequency of shoulder dysfunction in patients hospitalized for pulmonary tuberculosis, to evaluate factors influencing its development, and to formulate a program to prevent the appearance of this complication.

All observers have noted that "frozen shoulder" is rarely seen below the age of 40. In this group of patients severe shoulder disability was confined largely to those over 40 years of age. There were only 2 patients between the ages of 30 and 40 years who had any limitation of motion of the shoulder (Grade II disability). Pain and stiffness only, (Grade I disability) however, was almost as common in the younger patients as in the older ones.

Patients who developed shoulder dysfunction usually did so at a time when they were either at complete or almost complete bed rest. This was usually during the first 6 months of their hospitalization. The initial episode of shoulder pain never occurred at a time when the patient's activities had been increased, although shoulder dysfunction frequently persisted even after the regimen of strict bed rest had been modified.

Frozen shoulder is more commonly seen in women than in men[2]. Although in this series the incidence was higher among the males, no conclusion regarding the relative frequency of this disorder in the two sexes can be drawn because there were few women over the age of 40 on the wards of this hospital, while many of the men studied were in the age group most susceptible to the appearance of shoulder disturbances. Other factors such as duration of tuberculosis, race, location of the pulmonary lesions, and modes of treatment had no apparent effect on the development of shoulder dysfunction.

There are numerous causes for shoulder pain. They have recently been well summarized by Coventry[1]. In this group of patients with pulmonary tuberculosis only three of these are applicable. These are: 1) visceral referred pain from diaphragmatic and pleural irritation, 2) prolonged immobilization of the upper extremities, and 3) degenerative lesions of the rotator cuff. Since the side of the shoulder disability frequently did not correspond to the side showing pulmonary involvement, and since shoulder pain frequently occurred in the absence of pleural or diaphragmatic involvement, it is felt that factors of visceral or referred pain are of less importance than prolonged immobilization and degenerative lesions of the rotator cuff. In the treatment of no other disease is the patient as constantly impressed with the importance of complete bed rest as in tuberculosis. Many of the patients are reluctant to move their arms for fear of aggravating the pulmonary disease. Proof of the importance of immobilization is the fact that in all patients who developed shoulder pain, the symptoms appeared at a time when they were confined to bed, and not at a time when their activities had been increased. Degenerative lesions of the shoulder cuff, while present at any age, are usually more severe in older patients, and probably account for the greater incidence of shoulder dysfunction in people over the age of 40 years.

Most of the patients with shoulder pain do not go on to develop limitation of motion of the shoulder, but recover spontaneously or are left with a chron-

ically painful shoulder. Some, especially those in the older age groups where the process of attrition of the rotator cuff has had a chance to progress further, do go on to develop periarthritis with limitation of movement. One of the most important factors in the development of the "frozen shoulder" appears to be disuse and inactivity of the arm, resulting in capsular inelasticity and stiffness of the shoulder. The role of the "periarthritic personality" has recently been emphasized[1,5] but this factor is very difficult to evaluate. Coventry[1] has stated: "Pain from whatever cause plus disuse plus the periarthritic personality equals periarthritis."

Since shoulder pain causes considerable distress to these patients and since it is a potential factor limiting their ability to resume a gainful occupation upon discharge from the hospital, steps should be taken to prevent the occurrence of this disability, and to treat it promptly and vigorously once it develops. It is frequently very difficult to improve the function of a frozen shoulder. Therefore the main effort should be directed at the prevention of shoulder dysfunction, and not at the treatment of the stiff shoulder, which has been allowed to develop gradually during the treatment of the tuberculous process. Because disuse of the arm appears to be one of the main causes of shoulder pain and stiffness, any plan aimed at preventing the appearance or progression of shoulder dysfunction should attempt to increase the activity of the upper extremities.

In order to prevent the appearance of shoulder disorders, it is suggested that a program of active shoulder exercises be instituted in all patients over 40 years of age who are hospitalized for the treatment of tuberculosis. It is probably not necessary to have a similar prophylactic program for the younger patients who are not likely to develop periarthritis. The patient should be taught to move his arm through the complete range of motion twice daily for 3 to 5 minutes, preferably under supervision, and the importance of moving his arm by himself should be emphasized frequently. This would not interfere with the prescribed limited activity in any but the most severely ill patients, and with present-day chemotherapy, few patients stay at complete bed rest for prolonged periods of time.

If in spite of this prophylactic program some patients should go on to develop shoulder dysfunction, an aggressive program of physical therapy designed to maintain and increase the range of motion of the shoulder should be initiated promptly. This should consist of active exercises supplemented by heat and analgesic drugs. Cortisone has been reported to be effective in the treatment of frozen shoulders[1], but should not be used in patients with tuberculosis, in view of its harmful effects on this disease. Manipulation and surgical intervention are rarely indicated in patients suffering from a serious systemic disease such as tuberculosis, since the shoulder disturbance is usually self-limited.

In view of the poor results obtained by any method of treatment, once a frozen shoulder has developed, the best way to insure that the patient leaves the hospital with normal shoulder function is actively to prevent the development of periarthritis, and not to await its appearance prior to initiating therapy.

Summary. 1. A group of 260 patients hospitalized for the treatment of pulmonary tuberculosis was surveyed in order to determine the frequency of shoulder disabilities and to evaluate

factors responsible for their development.

2. It was found that the incidence of limitation of motion of the shoulder was low under the age of 40 (1.6%), but was high in patients over 40 years of age (24.2%).

3. Shoulder symptoms invariably developed while the patient was at complete or almost complete bed rest, although they frequently persisted after his activities had increased. In most instances symptoms developed during the first 6 months of bed rest. None of the other factors studied was found to influence the onset of shoulder dysfunction.

4. Since disuse of the upper extremity is postulated to be one of the more important factors in the development of shoulder disability, and since the treatment of frozen shoulder is difficult and frequently unsuccessful, it is suggested that a program of shoulder exercises be instituted for patients over 40 years of age who are hospitalized for the treatment of pulmonary tuberculosis, in order to prevent the occurrence of this complication, and to treat it vigorously and rapidly if it should develop in spite of this.

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A NEW APPROACH TO NIGHTTIME SEDATION

By Ella Roberts, M.D.
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Sleeplessness, one of the most common of modern complaints, is also one of the most difficult to treat, for sleep disturbances are usually accompanied by psychic factors which act as powerful antidotes to medication. The anxious fear of sleeplessness and the fear of drug dependence are two frequently encountered mental barriers to sleep.

Both hypnotics and sedatives are used successfully in treating sleep disturbances. Hypnotics produce sleep, sedatives induce sleep. Physically-caused insomnia (resulting from pain, cough, fever, and the like) is best treated with hypnotics. For most patients, however, a suitable sedative is the treatment of choice. Small doses of phenobarbital provide an excellent sedative, and for this reason the drug is widely prescribed.

Recently a new preparation* became available which encapsulates minute granules of phenobarbital and gradually releases the drug over a 10- to 12-hour period. Since sleeplessness gives rise to fear, and fear (of drug dependence, and of the supposed evil consequences of insomnia) increases sleeplessness, Myerson[1] has suggested that if the patient can disassociate the taking of medication from the induction of sleep these fears can be eliminated or alleviated. It was thought that the new preparation might prove of value in breaking this vicious cycle. Accordingly, over a period of 6 months, 21 patients (5 male, 16 female) suffering from sleep disorders were treated with the medication.

Material and Method. All patients included in this series had a pressing need for some soporific. Some had a serious organic disease, others suffered from mental tensions which produced insomnia. All had been receiving large doses of various hypnotics and sedatives, and all were dissatisfied with the results obtained by these drugs. Their chief complaint was that the use of a dose heavy enough to produce sleep resulted in difficulty in awakening, morning lethargy, and "heaviness".

The sustained-release capsules come in 1-gr. and 1½-gr. strengths which are equivalent to doses of ¼ gr. q.i.d. and ½ gr. t.i.d. respectively. The doses used were determined by the patients' needs. Initially, 8 patients received the 1-gr. capsule; 13 received the 1½-gr. capsule. Six of the 13 patients who were started on the 1½-gr. capsule switched to the lower dose; 4 patients occasionally (about twice a month) increased the dose to 2½ gr. (a 1-gr. capsule in addition to the original 1½-gr. dose).

The patients were instructed to take the capsule 45 minutes before retiring. They were told to take it on alternate nights only, if possible, and to omit taking it as often as they felt they could do without it. After each visit, a record was maintained of the amount of the drug currently available to each patient. The patients' reactions were also recorded, and at the end of 6 months all records were summarized.

Results. Of the 21 patients, 2 reported the customary insomnia in spite of the drug. In the remaining 19 patients the results were quite satisfactory. Eight patients who had previously required as much as 4½ gr. of other barbiturates received equal benefit from 1½ gr. of sustained-release phenobarbital. Eleven patients who, in spite of heavy doses of hypnotics, complained of waking in the early morning hours achieved a longer sleep with much fewer periods of wakefulness.

Almost all patients found, as the study progressed, that the use of a sedative became less and less neces-

*Eskabarb Spansule Capsules, Smith, Kline & French Laboratories.

sary. At the end of 3 months, 7 patients had stopped the medication entirely; 9 took it about 4 or 5 times a month. Three patients found it necessary to take the capsule nightly.

The general response of these patients was quite good. None reported morning depression or the heavy feeling typical of the barbiturate hangover. Many patients commented on the fact that the medication did not produce overwhelming bedtime drowsiness or morning confusion. The response was well summarized by one patient who reported: "This capsule doesn't compel me to sleep; it prepares me for sleep."

The following abbreviated case histories illustrate typical patient response to the medication.

Case Reports. CASE 1. A 67-year-old white female suffering from arteriosclerotic heart disease with myocardial infarction found, after being discharged from the hospital, that she was unable to sleep for more than one hour. Waking was accompanied by heart consciousness and a feeling of terror. She was given the 1-gr. sustained-release capsule 45 minutes before retiring. The medication was not immediately effective, but after several days resulted in a gradual lengthening of sleep. The patient can now sleep for 6 or 7 hours and no longer experiences terror upon awakening.

CASE 2. A 72-year-old white female suffered a crush fracture of the eleventh and twelfth dorsal vertebrae. During her hospital stay she received frequent and heavy doses of various soporifics. She could not sleep unless given an unusually large dose, which resulted in confusion and disorientation. The 1½-gr. sustained-release capsule, given 45 minutes before retiring, enabled her to sleep soundly without producing any ill effects.

CASE 3. A 47-year-old white female suffered from an acute relapse of rheumatoid arthritis. Although her treatment gave her fairly adequate relief from pain, she found it almost impossible to obtain sleep. Heavy sedatives produced confusion, lighter sedatives were ineffective. The 1-gr. sustained-release capsule provided her with adequate and restful sleep. She was given the medication nightly for the first 4 weeks; then 4 times a week for the next 6 weeks. As the acute arthritic episode subsided, she discontinued the medication.

CASE 4. A 46-year-old white female with rheumatic heart disease was on maintenance digitalis and mercury. She slept poorly and awakened several times a night with orthopnea. Various sedatives, which she had taken for years, had been of little value. By taking a 1½-gr. sustained-release capsule 45 minutes before retiring she has managed to achieve an adequate amount of sleep. Although she still occasionally awakens at night, she does so much less frequently.

Discussion. The most interesting result of the study was the disclosure that patients who had not responded well to heavy doses of powerful hypnotics achieved a refreshing and adequate sleep with smaller doses of a less potent drug. This response may, perhaps, be explained in two ways:

First, the capsule, because it is taken 45 minutes before retiring, is not as closely associated in the patient's mind with the usual more or less elaborate ritual the treatment of insomnia often takes. By eliminating the props of the ritual (the pills, the glass of water, the clock, all carefully arranged on the night table) the patient's preoccupation with the ceremonies of sedation is avoided; consequently, anxiety and fear of insomnia are lessened.

Second, the sustained-release preparation results in a more natural onset of sleep. The first released dose of the drug causes relaxation and mild sedation which prepares the patient for sleep, the following doses gradually induce sleep and, because the drug is released in minute, carefully determined doses; the patient awakens normally, free from the ill effects of oversedation.

It would seem, then, from the results of the study, that the sustained-release phenobarbital capsule is an effective means to provide adequate nighttime sedation.

Summary and Conclusion. A sustained-release preparation of phenobar-

bital was evaluated for 6 months in 21 patients who, because of organic disease or mental tension, suffered from sleep disturbances, and who had failed to respond satisfactorily to heavy doses of various barbiturates. The patients were seen at regular intervals when records of the number of capsules dispensed and the patients' reactions to the medication were made. The dose was tailored to the patients' needs; the medication was taken 45 minutes before bedtime.

Of the 21 patients, 2 were not helped by the medication; 19 were. In these 19 patients the use of the capsule resulted in a longer, more refreshing sleep free from barbiturate hangover. Better results were obtained with lower doses of the medication than had been obtained with heavy doses of more potent drugs. Four case histories are given which illustrate these results.

The beneficial action of the preparation is attributed first to the fact that the medication, because it is not given immediately before retiring, helps the patient to disassociate the taking of medication from the induction of sleep, and consequently, reduces the patient's anxiety and fear of sleeplessness; second, to the success of the capsule in maintaining a constant therapeutic drug level which results in a more natural sleep and lessens the possibility of oversedation.

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DIABETIC NEUROPATHY: CONTROLLED THERAPEUTIC TRIALS

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Involvement of the nervous system in patients with diabetes mellitus occurs with great frequency. Estimates of the incidence of diabetic neuropathy range from 5 to 93% in various groups of patients[4,6,7,11]. Among diabetics studied at Temple University Hospital, 51.7% were found to have neuropathic disorders not attributable to any other cause. The principal neurologic disturbances are found in the peripheral nervous system, particularly the sensory and motor supply to lower extremities and other areas, as well as the autonomic system. The purpose of the present report is to record the effects of a variety of treatments employed in several groups of patients with diabetic neuropathy.

Many clinical descriptions have been recorded of the variegated manifestations of diabetic neuropathy. Of the several types recognized, the first and most frequently encountered is the reversible, early, *mild* or hyperglycemic stage of the disease. As a classification, this is not entirely satisfactory, since an early or mild neuropathy may not be associated with hyperglycemia. The more serious stages of neuropathy are classified as *moderate* and *severe*, depending upon the degree of involvement. Any of these stages may be encountered (1) in poorly controlled diabetes, (2) in patients recovering from diabetic coma, (3) in those undergoing treatment for the first time, (4) in patients with ischemia affecting the extremities, and (5) rarely in mild diabetics in whom metabolic control has been easily maintained (these are usually "new" cases as in [3]).

The treatment of diabetic neuropathy has been satisfactory usually in those with early involvement. This consists simply in establishing careful stabilization of the diabetes with insulin and a diet providing a high protein intake and adequate calories to prevent weight reduction. Occasionally, neuropathic symptoms appear for the first time following the institution of diabetic treatment; in others, an apparently early neuropathy will progress temporarily, despite appropriate antidiabetic measures. However, with few exceptions, the earlier neuropathic cases are benefited by careful diabetic control.

In the moderate or severe cases the condition does not always respond readily to this program, so that various substances have been recommended in their management. Among these are vitamin B_{12}[6,12], pregnant mammalian liver extract[5], and adenosine triphosphate with thiamine. The present report is an evaluation of our experiences with each of these in the treatment of diabetic neuropathies.

Method and Material. The evaluation of the therapeutic efficacy of any treatment of

diabetic neuropathy requires the establishment of adequate criteria upon which the diagnosis, stage of the process, and progress during treatment can be based. Subjective manifestations such as neuritic pain, paresthesia, hyperesthesia are important, but may be misleading for comparison, since the patient may be susceptible to the investigator's enthusiasm. The objective signs of vibratory sensation diminution, hyperesthesia or reduction of pain and light touch sensations, reduced deep tendon reflexes, and muscle atrophy offer more satisfactory methods for critical analysis. The "double blind" technique of study is also desirable in assuring results uninfluenced by the observer.

In initiating these therapeutic trials, 37 patients with symptoms of diabetic neuropathy were given a period of adequate diabetic treatment with maintenance of relative normoglycemia and aglycosuria. Approximately two-thirds of the patients failed to respond to the program of metabolic control and were the subjects of therapeutic trials with the agents under investigation.

VITAMIN B_{12}. We began initially to administer Vitamin B_{12} in doses of 10 micrograms a day to patients with diabetic neuropathy using both oral and intramuscular routes. This dosage was increased to 30 micrograms intramuscularly daily when no response was observed with smaller doses. The daily injections were usually given over a period of 10 days to 3 weeks, then given twice weekly. Because of our failure to obtain improvement, the dosages employed were increased to 100 micrograms and, finally, to 1000 micrograms daily in several patients. Intensive treatment schedules were conducted in 12 patients with moderately severe neuropathic disturbances not responsive to routine diabetic management, including supplementary B complex vitamins. During recent months, we have seen 6 patients who have received similar treatment from other sources without benefit.

PREGNANT MAMMALIAN LIVER EXTRACT. In order to evaluate the effect of this agent we were provided with 6 series of unlabeled 50-cc. vials, some containing pregnant mammalian liver extract* and others containing the inert control solution colored to resemble the extract. The vials were lettered in series from A to F; the key to these symbols was not available until all results were tabulated. The patients selected for this study included only those who had not responded to a period of adequate metabolic control; several of them had previously received Vitamin B_{12} without benefit. All patients were examined by the Neurological Service before and after the treatment schedule. In each instance, well-established signs of neuropathy were present and all patients had symptoms referable to this process. Three of these patients had complaints which indicated the presence of autonomic nervous system disturbances, including diarrhea, or orthostatic hypotension.

Sufficient material was provided to conduct adequate treatment courses on a total of 15 patients. It was recommended that 5 cc. of the solution be injected intramuscularly daily for a period of 10 days to 2 weeks and then 5 cc. twice weekly for 4 to 6 weeks. In severe cases, 10 cc. was recommended as the dose for the initial 2-week period. During the course of observations, several other patients were treated with the commercially available product in the same way. All of the patients were admitted to the hospital for the initial treatment period of daily injections. Diabetic control was maintained satisfactorily with two exceptions, these patients having unstable diabetes with fairly wide fluctuations of blood sugar and glycosuria despite constant conditions.

ADENOSINE TRIPHOSPHATE, PLUS THIAMINE AND PANTOTHENIC ACID. Several reports have appeared indicating that the administration of adenosine triphosphate (ATP) together with thiamine produces prompt improvement in certain neurological disorders[3-8]. The combination of ATP and thiamine has been given on the premise that the high energy phosphate derived from ATP would be available for the rapid formation of thiamine pyrophosphate. This coenzyme is necessary for the decarboxylation of pyruvate in carbohydrate metabolism, the primary source of energy for nerve tissue.

With respect to pantothenic acid, it has been established that the formation of coenzyme A requires ATP and this vitamin. This coenzyme is important in the metabolism of acetate derived from carbohydrate, fat or protein sources for the production of energy by the tricarboxylic acid cycle[9]. It is also essential in certain transacetylating reactions, such as the formation of acetylcholine. The latter compound is one of the principal neurohumoral factors operating in nerve impulse transmission.

Six patients received treatment with ATP†, 25 mg., together with thiamine, 20

*Biohepulin: International Biochemical Corporation, Brooklyn, N. Y.

†Supplied by the Research Laboratories, The National Drug Company, Philadelphia 44, Pa.

mg., intramuscularly twice daily for periods of 2 to 4 weeks. The injections were continued twice weekly in 3 instances on an outpatient basis for periods of 4 additional weeks.

Four patients with diabetic neuropathy were treated with ATP, 25 mg., and pantothenic acid, 10 mg., intramuscularly twice daily for a period of 3 weeks. Observations upon the neurological status of these patients and those receiving thiamine and ATP were made by members of the Neurology Department (Dr. S. F. Gilpin).

Results. Evaluation of the effects of treatment consisting solely of careful diabetic control disclosed that the best results achieved were obtained by these measures. It is realized, of course, that if these patients had been treated with one of the agents under investigation the benefits might have been attributed to it. Of the 37 patients, there were 12 who were markedly relieved of symptoms with amelioration of the objective signs in most instances. Adjunctive vitamin B complex therapy had been withheld so that treatment had consisted solely of diet, insulin and rest. One of these had experienced approximately 80% improvement; he obtained no further benefit when given 30 micrograms of Vitamin B_{12}, and later, Vitamin B complex daily. Another had an early relapse of symptoms upon voluntary cessation of diabetic control for 3 months. Her neuropathic manifestations subsided within a period of 10 days following restabilization of diabetes. A third patient of this group noted the onset of neuropathy after treatment of diabetic acidosis but experienced improvement during the subsequent period of treatment. It was interesting to find that she, a young, new diabetic, had exacerbations of cutaneous hyperesthesias when the blood sugar was elevated transiently during the early period of stabilization.

VITAMIN B_{12}. During the course of administration of Vitamin B_{12} to 12 patients on an intensive dosage schedule, no significant subjective or objective manifestations of improvement were observed. One of our patients, of considerable interest, developed diabetic neuropathy 2 months after the institution of treatment for mild diabetes. He noted neuritic pain, paresthesias, muscle weakness, and rapidly progressed with manifestations of absent vibratory sensation, absent patellar and ankle deep tendon reflexes, muscle atrophy and foot drop. During most of 3 months' period of deterioration, the patient had received intramuscular Vitamin B_{12}, 30 micrograms daily, and oral Vitamin B complex supplements. Another patient developed severe diabetic neuropathy immediately following her recovery from a profound diabetic coma. This patient was given 30 to 100 micrograms of Vitamin B_{12} daily without improvement over a period of one month. Less dramatic cases of stationary nonprogressive diabetic neuropathy occurring as a result of poor metabolic control have not improved as a result of treatment with this agent. In his excellent review of diabetic neuropathy, Rundles[11] has stated that Vitamin B_{12} has been of no value in the therapy of this condition. Other authors have had similar experiences[7].

PREGNANT MAMMALIAN LIVER EXTRACT. The results of this study were disappointing, in that no patient manifested objective improvement in the sensory modalities (vibratory, pain and touch) or in motor function. Subjective improvement was striking in three of the patients; two of these were found to have received the control solution, and one had received the special liver extract. The visceral neuropathies were not improved. There were no local or systemic toxic effects noted and the course of diabetes in these patients was unaffected.

The original studies with pregnant mammalian liver extract indicated that 94% of 127 patients treated showed good or excellent results[5]. These results were at the subjective level, with little or no change observed in the objective manifestations except for improvement in vibratory sensations. In our limited group we have been unable to duplicate these findings and will have to continue the study with larger numbers of patients.

ADENOSINE TRIPHOSPHATE. In the use of this agent, the dosage schedule was derived from reports dealing with previous therapeutic programs in which a beneficial effect was noted within 2 weeks[3,8]. However, the results obtained were not impressive; no significant change was observed in the objective manifestations of the neuropathic disorder. It is of interest that one patient was able to return to his occupation for the first time in 1½ years, 6 weeks after treatment with ATP and thiamine, but showed no change in his objective signs. Subjective improvement was marked. Another patient showed striking subjective improvement in the neuropathy and noted the disappearance of nocturnal leg pains which we have regarded as a disorder of muscle physiology primarily[13]. Mild local reactions occurred at the site of ATP injections in most of the patients, but this was not of sufficient severity to interfere with treatment.

Discussion. The neurological syndromes encountered in diabetes mellitus present a most perplexing problem with respect to their pathogenesis and treatment. It is an unfortunate fact that the disabling symptoms of neuropathy may bring the negligent patient back to the physician only to find that relief cannot be afforded him. In one such instance in this series it was necessary to perform bilateral chordotomy in order to alleviate neuritic pain.

The improvement in combined sclerosis of pernicious anemia following treatment with Vitamin B_{12} led to its use in the management of various neuritides. An early report by Bean indicated a rapid subsidence of neuritic symptoms in 4 cases of peripheral neuritis with this agent[2]. Subsequently favorable reports appeared from several sources dealing with effect of Vitamin B_{12} in diabetic neuropathy[6,12]. The beneficial action of this vitamin in reversing the neurological changes associated with pernicious anemia is unexplained. Likewise, no information is available concerning its action in diabetic neuropathy.

Vitamin B_{12} plays a role in transmethylation, important in relationship to choline and methionine metabolism. Choline is a constituent of the phospholipids, lecithin and sphingomyelin, found in the myelin sheaths of myelinated nerves. The availability of single carbon groups for adenosine and nucleic acid synthesis may depend upon the action of Vitamin B_{12}[1]. Since the function of nerve cell bodies is related to the latter, and that of the axons to the former, a basis for its use in diabetic neuropathy can be hypothesized. However, there is no clinical evidence of Vitamin B_{12} deficiency in these patients, nor are there data to indicate that the biochemical actions of the vitamin can be enhanced by supplying an excess.

Precisely the same questions may be raised with respect to adenosine triphosphate and thiamine. It has been suggested that the increased availability of high energy phosphate and an enhanced rate of cocarboxylase formation may be effected by such treatment. However, there is no evidence of a defect in this phase of cellular metabolism in diabetic neuropathy. Furthermore, it is very doubtful that ATP will find its way into cells to function as a

phosphate donor for thiamine. Dephosphorylation of ATP may occur in the blood as a result of serum phosphatase activity[10].

In an effort to enhance the rate of coenzyme A production, the combined use of ATP and pantothenic acid was attempted; however, the same objections may be advanced as in the study with thiamine, namely, that there is no deficiency of energy production nor of coenzyme A formation in these patients, and that ATP does not get into the cells when injected in this fashion.

In the patients with diabetic neuropathy who have not responded to careful regulation of diabetes, none of the agents employed in the treatment has produced significant beneficial effects in the observations recorded in this study. In evaluating the results of treatment of this disorder, the physician must first appreciate that the clinical improvement which he may observe in a given case is likely to be the effect of careful regulation of the metabolic disturbance. In those patients with reversible neuropathy, the administration of a high protein diet with an adequate caloric intake to prevent weight loss will generally, although not always, bring about improvement, when combined with appropriate insulin therapy to maintain normoglycemia. Occasionally and inexplicably, neuropathy may become clinically manifested following treatment. When the satisfactory regulation of nutrition and blood sugar fails to improve the neuropathy, we have rarely encountered benefit from the use of the various agents investigated in this report.

Summary. There is presented an evaluation of several forms of treatment employed currently in patients with diabetic neuropathy, including Vitamin B_{12}, pregnant mammalian liver extract and adenosine triphosphate with thiamine or pantothenic acid.

Prior to the administration of these agents, control of diabetes with insulin and diet produced improvement or complete remission in patients with early or mild neuropathy. However, in some instances, the neuropathic disturbances progressed or remained stationary after treatment. Treatment of diabetes in newly diagnosed patients occasionally was associated with the development of neuropathy.

The more severe neuropathies, usually found in poorly controlled patients or occurring after treatment of diabetic coma, did not respond to adequate treatment of diabetes. It was in these patients that therapeutic trials with the above agents were performed. Vitamin B_{12} was administered to 12 patients, with failure to observe improvement in their neurological disorder. Pregnant mammalian liver extract was equally ineffectual in 15 patients. Subjective improvement in 3 patients of this group was noted; however, two of these were found to have received a placebo preparation used in this phase of the study. Adenosine triphosphate with thiamine produced subjective improvement in 2 of 6 patients so treated. No effect was noted in the group receiving pantothenic acid. There was no alteration in the objective manifestations of neuropathy with the use of the agents employed.

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SERUM LIPOPROTEIN PATTERNS IN A GROUP OF ELDERLY DIABETICS

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Individuals with diabetes mellitus are known to be affected with atherosclerosis both prematurely and in more severe degree as compared with the nondiabetic population. In this study the relationship between the estimated degree of such atherosclerosis as judged by the clinical syndromes resulting therefrom and the level of the serum lipoproteins was determined in a group of 41 elderly diabetics.

Method. All the patients in this study were drawn from a chronic disease hospital.* Those who were selected were under fairly good diabetic control and none were acidotic at the time of sampling or had recently been in coma; 27 were females, 14 males.

Blood samples were drawn in the fasting state before the administration of the morning insulin. These samples were then centrifuged and the serum drawn off into a fresh tube which was then placed in a refrigerator at 4° C. After a variable period of storage at this temperature of from 1 to 5 days, the specimens were forwarded to the laboratory where the determinations were performed. The ultracentrifuge patterns were determined according to the technique of Gofman *et al.*[6].

The decision to obtain all specimens in the fasting state was made following a preliminary study of the effects of fat feeding on lipoproteins. A total of 21 patients were each given one-quarter of a pint of sweet cream (120 cc.) and blood samples were obtained 4 hours after ingestion. The values of the serum lipoproteins in this postalimentary blood sample were compared with fasting samples which were obtained in the same patients the next morning after approximately a 12-hour fast. Significant effects were observed upon all classes of lipoproteins. There was, however, a very distinct quantitative difference between the higher density and lower density aggregates. S_f 11-21 and 21-35 were affected to a much lesser degree than S_f 35-100 and S_f 100-400. The postalimentary blood levels of S_f 11-21 and 21-35 were within ± 10% of the fasting control values in approximately one-half of the patients studied. Of the remainder, the majority showed variation from the control level of ± 50%. In general, the postalimentary values in all groups were higher than the fasting levels; however, there were several which were significantly lower. Within the S_f class 35-100, the levels of the postalimentary samples varied from control levels by more than ± 50% in 17 of the 21 studied, 5 patients showing an elevation of more than 200%. All patients in the S_f 100-400 class, showed a var-

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iation of more than 50%, the majority of these being greater than 200%.

In view of the effect of the alimentation of cream upon all of the S_f classes studied, it appeared desirable to obtain fasting blood samples in all cases. This view is somewhat at variance with that of other observers[6].

Results. After many unsuccessful attempts to grade the degree of atherosclerosis of our patients by reference to some total estimate of involvement, it was decided to achieve a grouping simply on the basis of the clinical syndromes which were displayed. Three groups were drawn up consisting of: 1) Those who showed evidence of marked atherosclerosis of the peripheral arterial tree and had sustained the loss of some member of a lower extremity. No distinctions were made between those with amputations of toes only as compared with more extensive loss of tissue. This group consisted of 14 patients, among whom were 2 with healed myocardial infarctions and 2 with cerebrovascular disease in addition to peripheral vascular disease. 2) Those patients who manifested only cerebrovascular disease. This group consisted of 16 patients. 3) Those patients displaying none of the aforementioned major manifestations of atherosclerosis. There were 11 patients in this third group. Insufficient numbers of individuals with coronary thrombosis as the sole manifestation of atherosclerosis were encountered in this population, and patients with this complication were not considered separately in this study. Inasmuch as renal diseases *per se*, regardless of etiology, may result in elevation of blood lipids, uremic patients were not included, nor those with clinical evidence of Kimmelstiel-Wilson syndrome.

Table 1 shows the mean values and range of variation observed among the classes of serum lipoproteins ranging from 11 to 400 S_f units, as calculated for each of the 3 groups. The statistical significance of these data has been determined by comparison of their means according to the Student table of "t" values. This statistical information is given in Table 2 in terms of "p" values.

From these tables it can be seen that statistically significant differences exist between the group with peripheral vascular disease and the other 2 groups but not between those with cerebrovascular disease alone and those with no major manifestations. The patients with peripheral vascular disease have higher levels of all classes of lipoproteins. However, when specific classes of lipoproteins are analyzed, it is seen that statistical significance of these differences is of the highest order in the S_f 35-100 class. Within the S_f 21-35 class, values are significant only when the peripheral vascular group (Group I) is compared with Group III (no major clinical manifestations). Though the mean concentration of lipoproteins in Class 11-21 is again somewhat higher in Group I than in either Groups II or III, the differences are not significant. The values in the class 100-400 are so similar that it is apparent that no real differences exist among the 3 groups.

Consideration of only males or only females did not yield information different from the combined data and hence has not been included. The average age of the patients in the 3 groups is seen to be very similar so that this is probably not a factor producing variance. The duration of the diabetes was next considered. The average duration in the 3 groups was 15.2, 10.5 and 13.3 years respectively, and these differences are not statistically significant. The severity of the diabetes, as judged by the insulin requirement, was found to be not widely different among the 3 groups. In general, those patients with peripheral

TABLE 1

	No. of Pat.	Sex	Aver. Age	Diabetes: Aver. Dur.	Diabetes: Aver. Sever.* 1+ to 4+	Urea N (mg. per 100 cc.)	Aver. Blood Pres.	Aver. Serum Lipoprotein (S_f Units) mg. per 100 cc.: 11–21	21–35	35–100	100–400
GROUP I											
Peripheral Vascular Disease	14	9 F 5 M	67 yrs	15.3 yrs	2.3+	26	160.7/82	72.5	78.57	85.35	13.35
Range of Variation			45–78 yrs	3–43 yrs		18–43		35–135	27–191	34–259	4–45
GROUP II											
Cerebrovascular Disease	16	10 F 6 M	69.4 yrs	10.5 yrs	2+	22	165/93.5	61.5	53.4	45.0	12.8
Range of Variation			51–82 yrs	2–21 yrs		15–35		17–104	17–101	7–104	4–19
GROUP III											
No Major Manifestations of Vascular Disease	11	8 F 3 M	67 yrs	13.3 yrs	1.8+	22	154.5/85	58.5	44.5	36.18	11.7
Range of Variation			45–78 yrs	6–29 yrs		15–40		29–112	24–72	10–79	4–30

* As judged by insulin requirement

vascular disease did show a somewhat more severe type of diabetes than did those in the other 2 groups.

Since blood lipid values may be influenced by the presence of renal disease, the blood urea values have been included. The means of the individual values of Groups II and III are the same, while that of the first group is slightly higher.

Blood pressure readings were available on all but 2 of the patients. These readings were obtained from the patient's chart and should be viewed as a casual sampling. The average systolic and diastolic pressures in the group with cerebrovascular disease are somewhat higher than the other 2 groups.

TABLE 2.—STATISTICAL SIGNIFICANCE OF THE DIFFERENCE BETWEEN THE MEANS OF THE THREE GROUPS

	S_f 11–21	S_f 21–35	S_f 35–100
Group I (PVD) vs. Group III (NMVD)	.2 p .1	.05 p .02	.02 p .01
Group I (PVD) vs. Group II (CVD)	n. s.	.2 p .1	.05 p .02
Group II (CVD) vs. Group III (NMVD)	n .s.	n. s.	n. s.

p = probability that the observed differences are due to chance, obtained by Student's "t" test
PVD = peripheral vascular disease
CVD = cerebrovascular disease
NMVD = no major vascular disease
n. s. = not significant

Comment. There have been several previous reports of blood lipoprotein values in diabetes[1-4,6-8]. These have attempted to furnish information concerning 3 basic questions; namely, whether lipoprotein levels are elevated in the diabetic population as compared with nondiabetics of similar age and sex, whether the severity, control and duration of diabetes is of significance, and finally, whether any clear correspondence between lipoprotein values and clinical atherosclerosis is present. Though data are scattered and not all studies have considered all 3 aspects of the problem, some tentative conclusions may be drawn. It is the consensus that the level of lipoproteins is somewhat elevated in the diabetic population taken as a whole[2,4,6,8]. The variation from normal however is slight, and since the range of "normality" is quite wide, most diabetics will fall within the "normal" range[3]. It is also generally agreed that those with clinical nephropathy will evince the highest levels among the diabetics[3,5,8]. There does not appear to be a correlation between lipoprotein levels of S_f 12-20 and arterial or aortic calcification, heart size, cardiovascular disease or any estimate of the total degree of atherosclerosis. However, in these studies no analysis of peripheral vascular disease in relation to lipoprotein values was attempted as was done in this present study, nor as far as can be ascertained, were substantial numbers of diabetics with peripheral vascular disease included in the general series studied. Finally, there is conflicting evidence concerning the relationship of lipoprotein levels to the severity, control or dura-

tion of diabetes and no conclusions are warranted at present.

The data gathered in this study of lipoprotein patterns in elderly diabetics have indicated that, on the average, higher levels are observed in those who have involvement of the peripheral vascular tree, with loss of tissue, as compared either with those who have sustained only cerebrovascular insults or those who have not had such complications. Statistical significance was observed, however, only in the S_f class 35-100. Of less significance was the difference observed in the S_f 21-35 class, and no significant differences were found in the S_f 11-20 class.

In the further study of this data, it was seen that the difference between the lipoprotein levels of Group I with severe peripheral vascular disease and Group II and Group III could not be accounted for by consideration of such other factors as sex difference, age difference, duration or severity of diabetes, presence of renal disease or hypertension.

If one may assume that in the presence of clinically evident peripheral vascular disease a greater degree of atherosclerosis exists than in the absence of clinical manifestations, then it would seem appropriate to state that the lipoprotein pattern reflects the degree of atherosclerosis. This, however, is recognized to be an assumption only and how it is possible, in humans, to estimate either the degree of total atherosclerosis or the rate of atherogenesis is difficult to image. It is not therefore appropriate, in our opinion, either to generalize these findings to all manifestations of atherosclerosis or to accept as a standard of reference some single clinical syndrome. This is shown by the fact that lipoprotein patterns of nondiabetic patients with healed myocardial infarctions studied by us[9] showed S_f 11-21 and S_f 35-100 levels which were in the range of Groups II and III of this study and hence much lower than those with peripheral vascular disease. It is possible that the variability found in determinations of the blood lipids in relation to atherosclerosis may represent the variability of individual susceptibility to specific clinical syndromes at different levels of disease rather than variability of the relationship of lipid concentration to total disease.

Conclusions. Serum lipoprotein determinations have been performed in a series of 41 elderly diabetics with a variety of clinical syndromes. It was observed that patients with peripheral vascular disease showed higher levels in the Class S_f 35-100 than were found in those with cerebrovascular disease alone or in those without peripheral vascular, cardiovascular or cerebrovascular disease. This relationship was shown to be statistically significant. The groups were shown not to be significantly different with respect to age, sex, duration or severity of diabetes, presence of renal disease or hypertension. Some implications of these findings are discussed.

The effect of cream ingestion upon the serum lipoprotein patterns of these individuals has been ascertained and the importance of obtaining determinations in the fasting state has been stressed.

ACKNOWLEDGMENT: The authors express their appreciation to Mr. Paul J. Geller for his technical assistance.

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The data gathered in this study of lipoprotein patterns in elderly diabetics have indicated that, on the average, higher levels are observed in those who have involvement of the peripheral vascular tree, with loss of tissue, as compared either with those who have sustained only cerebrovascular insults or those who have not had such complications. Statistical significance was observed, however, only in the S_f class 35-100. Of less significance was the difference observed in the S_f 21-35 class, and no significant differences were found in the S_f 11-20 class.

In the further study of this data, it was seen that the difference between the lipoprotein levels of Group I with severe peripheral vascular disease and Group II and Group III could not be accounted for by consideration of such other factors as sex difference, age difference, duration or severity of diabetes, presence of renal disease or hypertension.

If one may assume that in the presence of clinically evident peripheral vascular disease a greater degree of atherosclerosis exists than in the absence of clinical manifestations, then it would seem appropriate to state that the lipoprotein pattern reflects the degree of atherosclerosis. This, however, is recognized to be an assumption only and how it is possible, in humans, to estimate either the degree of total atherosclerosis or the rate of atherogenesis is difficult to image. It is not therefore appropriate, in our opinion, either to generalize these findings to all manifestations of atherosclerosis or to accept as a standard of reference some single clinical syndrome. This is shown by the fact that lipoprotein patterns of nondiabetic patients with healed myocardial infarctions studied by us[9] showed S_f 11-21 and S_f 35-100 levels which were in the range of Groups II and III of this study and hence much lower than those with peripheral vascular disease. It is possible that the variability found in determinations of the blood lipids in relation to atherosclerosis may represent the variability of individual susceptibility to specific clinical syndromes at different levels of disease rather than variability of the relationship of lipid concentration to total disease.

Conclusions. Serum lipoprotein determinations have been performed in a series of 41 elderly diabetics with a variety of clinical syndromes. It was observed that patients with peripheral vascular disease showed higher levels in the Class S_f 35-100 than were found in those with cerebrovascular disease alone or in those without peripheral vascular, cardiovascular or cerebrovascular disease. This relationship was shown to be statistically significant. The groups were shown not to be significantly different with respect to age, sex, duration or severity of diabetes, presence of renal disease or hypertension. Some implications of these findings are discussed.

The effect of cream ingestion upon the serum lipoprotein patterns of these individuals has been ascertained and the importance of obtaining determinations in the fasting state has been stressed.

ACKNOWLEDGMENT: The authors express their appreciation to Mr. Paul J. Geller for his technical assistance.

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THE RISK OF MAJOR SURGERY IN PATIENTS WITH CORONARY ARTERY DISEASE

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The risk of surgery in patients with coronary artery disease is a problem of growing importance to both the internist and surgeon. The prevalence of coronary artery disease is increasing not only because of our aging population, but also because the life expectancy of the patient with angina pectoris or myocardial infarction would seem to be greater than it was 10 or 15 years ago. Consequently increasing numbers of patients with coronary artery disease are presenting themselves as candidates for surgery.

Until recently the patient with coronary artery disease was usually considered such a poor operative risk, that surgery was attempted only under compelling circumstances. In 1930, Butler, Feeney, and Levine[2] reported a mortality rate of 7.7% in 41 operations on patients with angina pectoris, and a mortality rate of 44.5% in 20 operations on patients with coronary thrombosis. However, Levine[4] recently has emphasized that this study no longer reflects the true risk of surgery in this group of patients.

Unfortunately, the information available on this subject is limited and no single institution has had sufficient experience to gather statistically valid conclusions. It is the purpose of this report to summarize the morbidity and mortality observations in 32 patients undergoing 51 major operations in this hospital during a 3-year period.

Material. The material for this study was obtained from the records of approximately 8,600 patients subjected to major surgical procedures in this hospital during the years 1950 to 1952. All of the procedures were carried out under general anesthesia and were concerned with thoracic, abdominal, gynecologic, neurologic or orthopedic surgery. Of this group of patients, 32 fulfilled the criteria for the diagnosis of coronary artery disease. These criteria were either unequivocal historical, electrocardiographic, or postmortem evidence of myocardial infarction, or a history of angina pectoris induced by exertion. It is recognized that there were many more than 32 patients with coronary artery disease operated upon during this period. However, only in those instances in which the available data clearly substantiated the diagnosis were the patients included in this analysis.

Results. The 32 patients fulfilling our criteria were subjected to a total of 51 surgical procedures. Thirty operations were performed on 17 patients with one or more episodes of myocardial infarction, and 21 operations were performed on 15 patients with angina pectoris. The operative and postoper-

ative morbidity and mortality in these two groups are summarized in Table 1.

In 30 operations performed on the patients who had previously experienced one or more myocardial infarctions there were 3 deaths. Each of these was attributed to the presence of coronary artery disease; two of the deaths proving at necropsy to be due to recent myocardial infarction while the other was due to progressive congestive heart failure. In each of these 3 subjects the preoperative evaluation revealed the presence of either recent myocardial infarction, or severe myocardial insufficiency as manifested by progressive angina and cardiac decompensation. The possibility that the 2 patients who died of recent myocardial infarction may have sustained coronary occlusion during the immediate preoperative period seems highly likely from review of the clinical record.

The only postoperative complication occurring in this group of patients was a brief episode of auricular fibrillation in one subject who underwent a cardiopneumonopexy for progressive angina. This arrhythmia responded promptly to the usual therapeutic measures. The remaining 26 operations on the patients with myocardial infarction were performed without operative or postoperative complication. It is pertinent that 15 of these uncomplicated operations were carried out on patients who were considered poor operative risks because of severe angina or the presence of congestive failure.

In the 21 operations performed on the subjects with angina pectoris, there were no deaths and only 2 postoperative complications; in each instance, episodes of congestive heart failure occurring postoperatively and responding promptly to appropriate treatment. There were no complications in the other 19 operations in this group in spite of the fact that 10 of the patients

TABLE 1.—THE OPERATIVE AND POSTOPERATIVE MORBIDITY AND MORTALITY IN PATIENTS WITH CORONARY ARTERY DISEASE, THE GEORGE WASHINGTON UNIVERSITY HOSPITAL

	Number of Patients	*Number of Operations*	*Operative Complications*	*Postoperative Complications*	*Number of Deaths*
Myocardial Infarction	17	30	0	1	3
Angina Pectoris	15	21	0	2	0
Total number of patients with coronary artery disease	32	51	0	3	3

TABLE 2.—SUMMARY OF RECENT REPORTS OF OPERATIVE AND POSTOPERATIVE MORBIDITY AND MORTALITY IN PATIENTS WITH CORONARY ARTERY DISEASE

	Angina Pectoris				*Myocardial Infarction*			
Author	*Number of Patients*	*Number of Operations*	*Number of Complications*	*Number of Deaths*	*Number of Patients*	*Number of Operations*	*Number of Complications*	*Number of Deaths*
Morrison[5]	41	58	1	5	25	37	1	3
Hannigan[3]					58	58		3
Lochhead, *et al.*	15	21	2	0	17	30	1	3
TOTAL	56	79	3 (3.8%)*	5 (6.3%)*	100	125	2 (1.6%)*	9 (7.2%)*

* Percentage of the number of operations

exhibited signs or symptoms of cardiac decompensation shortly before surgery.

In Table 2 we have tabulated our results and those of two recent papers by authors using essentially the same diagnostic criteria employed in this study. Attempts at comparison and evaluation are hampered not only by the scarcity of medical literature on this subject, but also by the difference in the diagnostic criteria used.

Discussion. Our observations, in agreement with other recent studies, seem to indicate that the patient with coronary artery disease does not pose as forbidding a surgical problem as was previously thought. In 1939, Brumm and Willius[1] reported 4.3% cardiac deaths among a group of 257 coronary patients undergoing major operations. Morrison[5], in evaluating this problem in patients operated upon at the New York Hospital from 1933 to 1943, found a mortality rate of 8.6% in 58 operations on patients with angina pectoris, and a mortality rate of 8.1% in 37 operations on patients with myocardial infarction. These figures, although higher than those of Brumm and Willius, included all deaths, whether they were related to the underlying cardiac disease or not. In 1951, Hannigan and associates[3], at Memorial Hospital in New York City, analyzed the records of 58 patients with healed myocardial infarction who underwent major surgical procedures and found a mortality rate of 6.3% in 79 operations in subjects with angina pectoris and 7.2% in 125 operations in subjects with myocardial infarction.

It is agreed generally that 3 to 6 months should elapse following acute myocardial infarction to permit optimal repair of the heart muscle prior to operation. In two of the fatal cases in our infarction group the postmortem evidence was consistent with fresh infarction, a fact prejudicial to the operative recovery of these patients and emphasizing the need for careful preoperative screening of patients to exclude recent coronary occlusion.

In reviewing this material, it was apparent that the average age of the patients was considerably higher than that of the general hospital population. Also, in many instances the indications for surgery were mandatory and relatively few of the operative procedures were elective in nature. All of these factors would contribute to a higher mortality in comparison with the non-coronary group.

It is noteworthy that despite the fact that the majority of these patients were poor surgical risks there were no complications during the operations that could be attributed to the heart disease, a tribute to current operative methods and anesthesiology. It is apparent that cooperation of the internist, surgeon and anesthetist was essential in the preparation of the patient for surgery and in the management of the operative and postoperative periods.

Summary. The morbidity and mortality observations are reviewed in 32 subjects with coronary artery disease undergoing 51 major operative procedures during the years 1950 to 1952. There were 3 deaths and one postoperative complication in 17 patients with myocardial infarction undergoing 30 operations; in 15 patients with angina pectoris undergoing 21 operations there were no deaths and 2 postoperative complications. There were no operative complications in either group of patients. These figures compare favorably with others recently reported and reflect the improved outlook for the patient with coronary artery disease undergoing surgery.

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COMBINED ELECTROLYTE THERAPY IN ADVANCED RENAL DISEASE MANIFESTED BY AZOTEMIA AND ACIDOSIS*

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The management of advanced renal disease manifested by uremia and acidosis is a serious medical problem. Control of infection, relief of obstruction and proper hydration are essential but at times not completely remedial. Recently newer methods of approach have been suggested including artificial dialysis[22,25,28], dietary protein restriction with forced caloric intake[5,24] and the correction of electrolyte abnormalities in the salt[30,56] and potassium-losing nephritides[6,9,11,47,52]. By daily measurements of the urinary excretion a careful approach of electrolyte replacement has been suggested by Sisson[50] and Newburgh[34].

Sporadic reports regarding the use of sodium bicarbonate or isotonic sodium lactate[18,60] for the correction of metabolic acidosis have appeared in the literature[20,27,36,37,57], but consistent clinical results did not occur. More recently, however, correction of renal acidosis with sodium bicarbonate has resulted in clinical and chemical improvement in the hands of certain investigators[7,12,13,42,45].

Potassium, although generally held contraindicated in uremia[14,44,51,55], at times has a definite place in therapy[6,11,52]. Calcium salts are beneficial in the relief of calcium depletion[3] in spite of the fact that acidosis tends to protect the ionizable fraction of the total calcium. When phosphate retention is evident calcium salts are postulated to be more effective when administered with aluminum hydroxide gel[48].

Within the past 30 months, 84 patients with advanced renal uremia have been studied with a combined electrolyte approach after all usual measures of therapy failed[31,32,33]. This approach, oral or intravenous, consisted of the administration of hypertonic sodium lactate (1 to ½ molar) 120 to 240 mEq., with 4 to 8 gm. of calcium gluconate or lactate (in Amphojel, when given orally) daily. Occasionally potassium used as acetate or chloride was employed as part of the regimen.

This approach was tried originally to further evaluate disturbances noted in deltoid muscle electrolytes in a series of biopsy analyses performed in patients with advanced renal disease[43]. In this series it was noted that there was a marked increase in tissue chlorides with a moderate decrease in tissue potassium. Sodium and water were slightly elevated but all the changes could not be explained on the basis of increased extracellular fluid in the specimen.

As Pitts was able to show that excess bicarbonate facilitated an excretion of excess chloride in the damaged kidneys of dogs[39], it was decided to

*This work was supported by a Grant from the National Heart Institute, Bethesda, Maryland.

see if a similar change could be accomplished in patients with terminal renal disease. Sodium lactate was used because it is a precursor to bicarbonate[3, 18], and the hypertonic concentration was selected because several of the initial cases had edema[38]. Calcium lactate or gluconate was used to prevent tetany which would be apt to occur with a rapid shift in the CO_2-combining power. At times added potassium in small doses was used cautiously, but not in all cases, to replenish the possible cell deficit noted in the tissue analyses.

The anticipated changes in chloride metabolism did not always occur, but since clinical and chemical improvement ensued in the first several cases, a further evaluation of this approach appeared warranted.

Certain chemical changes were of note, namely, a fall in the blood urea nitrogen, with a frequent over-correction of the CO_2-combining power and a reciprocal fall in the extracellular chloride level. These changes appeared to be correlated with clinical improvement of varying degrees in most of the initial cases studied.

It is the purpose of this paper to relate changes in the blood urea nitrogen values and to describe alterations in the structure of the extracellular fluid resultant from the administration of these electrolytes. Twenty cases comprise this first series. These include 11 cases of chronic glomerulonephritis, 4 cases of chronic pyelonephritis, 2 cases of polycystic kidney disease and 3 cases of hydronephrosis with post-obstructive uremia.

Cases and Methods. The proper selection of patients for this regimen was of utmost importance. The study was necessarily limited to those patients who received no benefit from other available forms of therapy. The factors of infection, dehydration, and obstruction were alleviated in all cases before the combined electrolyte approach was begun. Patients who improved with correction of the above factors or with protein restriction and forced calories were excluded from the series. All patients were believed to be critically ill. The non-comatose patients were experiencing signs and symptoms of uremia and had marked diminution of renal function tests. In the non-comatose cases studied renal disease had been known from 2 to 17 years and in the group with chronic glomerulonephritis who were ambulatory 5 year antecedent data were available.

Of prime importance in the selection of cases was a mutual agreement with the attending physician that the patient had received all other available forms of therapy without benefit and that the patient's condition was critical. Therefore, should a patient expire during the period of observation or under electrolyte treatment, no discredit or blame could be directed at the electrolyte regime.

MINIMAL BASELINE DATA. As many baseline data as possible were collected on each case. These ranged from 48 hours to 4 weeks depending upon individual circumstances, excepting 2 moribund cases.

In non-comatose patients, data were accumulated while they received a 1.0 gm. salt, 20 to 40 gm. protein diet with forced calories. During this time fluid intake was kept between 2500 and 3000 cc. since all cases had a good urinary output. If this intake could not be maintained orally supplementary intravenous fluids were ordered at the discretion of the attending physician. In many instances diets were weighed before and after serving so that an estimation of ingested electrolytes[4] was available. Correction for stool or sweat electrolytes was not made since the renal handling of electrolytes was of major interest at the time.

All intake-output data were collected on a 24-hour basis from 7 a.m. to 7 a.m. The total fluid intake was carefully measured and 24-hour urines were collected, measured and analyzed for sodium, potassium and chloride. When possible patients were weighed upon arising each morning. Routine urinalyses were done on the first voided sample daily for 3 days and then weekly. Several urine cultures were done on all cases.

Analyses were done daily for blood urea nitrogen[21], serum sodium, potassium[15], chloride[16] and CO_2-combining power. Less frequent determinations were performed for calcium, phosphorus, sedimentation rate, total proteins, and A/G ratio and cholesterol.

Complete blood counts, chest roentgenogram and electrocardiogram were followed closely. Should edema be present, circulation time and venous pressure were measured.

The blood pressure was measured at least 2 times daily during the periods of salt restriction and also during the periods of sodium administration. Close clinical observations were made for edema formation and these were correlated with daily weight since space volume measurements were not available.

Phenolsulfonphthalein dye excretion, and, when possible, urea clearance were done upon discharge and repeated every several months as an outpatient.

PROTOCOL. This protocol as outlined was strictly adhered to in relation to time schedule and dosage of fluid and electrolytes (deviation from this outline did not produce similar results).

This protocol may be divided into 2 parts: treatment of non-comatose patients and treatment of comatose cases.

Electrolyte Therapy in Non-Comatose Patients. Since the management of a patient rousing from coma able to tolerate fluids, food and oral medication is essentially the same as therapy in this above group, this schedule will therefore also refer to patients responding from coma, the only difference being in the diet.

Patients who were not comatose were selected for this study if they had a urea clearance of below 5 to 10% of normal and a phenolsulfonphthalein excretion of less than 10% total while experiencing signs and symptoms of their disease. During the dietary management, the blood urea nitrogen value was followed until it remained unchanged. Then a 10% suspension of calcium lactate in Amphojel and when necessary one molar potassium acetate in syrup were added to ascertain the effect of these electrolytes upon the blood urea nitrogen. When no change occurred in the blood urea nitrogen value, one molar sodium lactate was begun. A rising blood urea nitrogen level and a falling CO_2-combining power was an idication for the earlier administration of sodium lactate.

The management of these patients in regard to oral electrolytes was as follows:

40 cc. 1 molar sodium lactate* 4 to 5 times daily.

20 to 40 cc. of 10% calcium lactate in Amphojel q.i.d.

When necessary, depending upon serum value and urinary output, 5 to 10 cc. 1 molar potassium acetate** 3 or 4 times daily.

Electrolyte Therapy in Comatose Patients. All therapy was given intravenously to those patients excepting one in whom a Levin tube was used (T.B.).

A. At 10 a.m. after baseline samples were drawn, 1000 to 1500 cc. of 5% glucose in water or 10% Travert† containing 2 to 6 gm. of calcium gluconate (10% solution) and 10 units of regular insulin‡ was administered in a 2 to 2½-hour period. Potassium as chloride or acetate was added to this infusion in the dose of 2 to 4 gm. only if the serum value was normal or below normal with adequate urine formation and stable circulation.

B. At 4 p.m. (never less than 3 to 4 hours after completion of the above infusion) 120 to 240 cc. of one molar sodium lactate** with 0.5 gm. aminophyllin and at times equal parts of 5% glucose in water to make a ⅓ molar solution. The amount of sodium lactate used depended upon a fall in the blood urea nitrogen level, that is, if an initial decrease did not occur or continue, the amount of sodium lactate was increased. Equal parts of glucose in water were used only when edema was absent and when no cardiac impairment was suspected. (Early in the study 3 cases received hypertonic sodium chloride because of a marked drop in the extracellular chloride value. This was administered as 150 to 250 cc. of 2½% NaCl with 40 to 120 cc. of 1 molar sodium lactate with 0.5 gm. aminophyllin from 1 to 4 days. The effect of this combination was uncertain since there was little change in the serum chloride value.)

C. At 10 p.m. (never less than 3 to 4 hours after completion of the hypertonic infusion) 1000 to 1500 cc. of 5% G/W or 10% Travert with 2 to 6 gm. of calcium gluconate and 10 U of regular insulin was given. Potassium in similar doses to the morning infusion was added to this only when necessary.

Should the patient rouse from coma with the above therapy, water, ginger ale, coke syrup, tea and sugar were begun orally. Total

*A special preparation of Robert Bogash, B.S. (Lennox Hill Hospital, N. Y.), available from Libby Drug Company, Wilmington, Delaware.

**Eli Lilly sodium racemic lactate available as a one molar solution in 40 cc. ampules. This was not used as the recommended dilution of 1/6 M.

†Baxter preparation — invert sugar.

‡Insulin was used in an attempt to move potassium into the intracellular compartment. It is also noted that in the early days of insulin it was also used in the treatment of renal acidosis.

fluids were maintained at 2500 to 3000 cc. with supplementary intravenous feedings. Salt free toast, butter, jelly and mashed potatoes were then begun along with hard candies. Oral sodium lactate and calcium lactate were begun as soon as tolerated and the diet was gradually increased to 20 to 40 gm. protein with 1.0 gm. salt. If vomiting or diarrhea occurred with institution of oral therapy, the patient was urged to repeat the dose in 20 minutes. Gastrointestinal irritation from the hypertonic solutions tended to disappear in several days.

Anemia was successfully controlled in certain cases with the administration of 100 to 200 mg. of cobalt chloride daily*[17]. Should the anemia not respond within a period of 14 days and it be felt advisable to attempt to correct this (which is not without danger in the patient with chronic renal disease) the following procedure was adopted. Packed red cells prepared from a fresh donor were obtained within 24 hours. Forty cc. of one molar sodium lactate was given intravenously, followed immediately by 100 to 150 cc. packed cells, again followed by 40 cc. of one molar sodium lactate. This was repeated every several days until a sufficient response was obtained. To date with this method, no side effects of transfusions have been noted.

Upon discharge the patient was maintained on the same regimen and followed initially at weekly intervals. As an outpatient, determinations were done for blood urea nitrogen, hemoglobin, serum sodium, potassium, chloride and CO_2-combining power. Each patient was instructed as to recording his own intake and output and weighed himself 3 times weekly in the morning upon arising. Twenty-four hour urine samples were collected by the patient and brought in for analyses for sodium, potassium and chloride weekly.

Maintenance therapy has been indicated in most of the cases studied, this being judged by renal function studies below 5 to 10% of normal or by a clinical and chemical deterioration upon withdrawal of electrolytes.

Results. Table 1 indicates that with a combined electrolyte regimen all the initial cases studied showed some decrease in the blood urea nitrogen value. This seemed to be directly related to this type of therapy since conventional forms of management had produced no significant chemical effect before the administration of hypertonic sodium lactate. At times the clinical changes were noted within several days but other patients needed more prolonged therapy. Maintenance therapy appeared indicated in the majority of initial cases studied. In most instances the blood urea nitrogen level remained in the lower levels as demonstrated. This does not indicate, however, that this was a permanent or indefinite trend nor does it indicate any improvement in actual renal function.

Clinically all cases showed some degree of improvement except in Case No. 10 (F.G.). Since the patient with advanced renal disease in a stable phase of the lesion may live indefinitely, overenthusiasm regarding clinical results must be avoided. From this study it appeared that life expectancy was prolonged. It is of interest that the patients who did improve were in the most part able to be almost completely rehabilitated.

In accordance with the findings of Salvesen[45] using alkaline therapy in uremia the 11 cases of chronic glomerulonephritis in this series were the most difficult to manage, although the chemical changes were favorable. Excellent clinical and chemical results were obtained in the 4 cases of pyelonephritis and in one case of polycystic kidney disease. The 3 cases of postobstructive uremia due to hydronephrosis all had excellent results and maintenance therapy was not necessary.

Case Reports. CHRONIC GLOMERULONEPHRITIS. CASE 1. T.H. was admitted to the hospital with a 3-weeks progressive onset of coma, 2 plus edema generalized. Twitchings were frequent and ecchymoses were scattered over the body. Mild hypertension was present. For 3 days the patient was treated with isotonic fluids and blood but his condition deteriorated. He was then begun on com-

*Cobalt chloride, prepared by Mr. Robert Bogash, B.S., made available by Libby Drug Company, Wilmington, Delaware.

bined electrolyte therapy and within 8 days displayed dramatic improvement. By mistake he received dextri-maltose containing salt (1000 calories daily) but in spite of the high sodium intake the patient completely lost his edema in 8 days with no diuresis. This suggested a large fluid shift and indicated that the volume of distribution of hypertonic sodium lactate must have been greater than the extracellular compartment since this patient retained about 1000 mEq. sodium during this 8-day period. When the patient's urea had fallen to 55 mg. per 100 cc., he was switched to oral sodium bicarbonate therapy with a gradual rise in the blood urea nitrogen to 85 mg. per 100 cc. The patient

TABLE 1

				Blood Urea Nitrogen				*Condition*	
Patient	*Age*	*Sex*	*Diagnosis*	*Before Electrolyte Treatment*	*Lowest*	*Time*	*Dose Na Lactate*	*Before*	*After*
1. T. H.	25	M	CGN	164	55	41 days	4800 mEq	comatose	improved
2. T. G.	29	M	CGN	110	10	12 days	2120 mEq	comatose	improved
3. P. E.	29	M	CGN	60	18	34 days	2760 mEq	ambulatory	improved
4. R. P.	30	M	CGN	70	30	10 days	1600 mEq	ambulatory	improved
5. S. M.	29	M	CGN	45	25	14 days	2800 mEq	ambulatory	improved
6. S. G.	29	M	CGN	180	70	5 days	700 mEq	semicomatose	improved
7. T. D.	30	M	CGN	75	40	7 days	200 mEq (S. I.)*	ambulatory	improved
8. L. S.	72	F	CGN	70	25	10 days	980 mEq	comatose	improved
9. A. H.	28	F	CGN	87.5	10	30 days	2920 mEq	ambulatory	improved
10. F. G.	48	F	CGN	180	75	30 days	2810 mEq	semicomatose	no change
11. G. S.	67	M	CGN	62.5	19	17 days	1040 mEq	semicomatose	improved
12. H. D.	56	M	CPN	237	11	30 days	4500 mEq	semicomatose	improved
13. R. F.	74	M	CPN	165	40	16 days	560 mEq	comatose	improved
14. W. W.	84	M	CPN	37.5	11	5 days	700 mEq	bedridden	improved
15. S. S.	61	M	CPN	67	34	18 days	2520 mEq	comatose	improved
16. A. H.	48	M	PC	130	95	10 days	1600 mEq	ambulatory	improved
17. M. Y.	56	F	PC	122.5	50	11 days	2200 mEq	comatose	improved
18. E. S.	31	M	HYDRO	130	10	9 days	1440 mEq	ambulatory	improved
19. W. S.	79	M	HYDRO	40	11	7 days	1120 mEq	bedridden	improved
20. J. C.	62	M	HYDRO	48	14	2 days	390 mEq	comatose	improved

CGN—Chronic Glomerulonephritis
CPN—Chronic Pyelonephritis
PC—Polycystic Kidney Disease
HYDRO—Hydronephrosis
* Single Injection

was then followed for one year on maintenance sodium bicarbonate and calcium therapy. He eventually died from a progressive hypertension. Whether or not this was related to a progression of the disease or to sodium ingestion is not clear. Other cases suggest that the sodium *per se* had little to do with this.

CASE 2. T.B. was a 29-year-old colored male who had carried 20 lbs. of edema for a 5-year period. Frequent episodes of confusion and puffiness of the face had been noted. He was admitted to the hospital in a critical condition with hypertension, cardiac dilatation and diarrhea simulating an acute exacerbation of chronic nephritis. Spontaneous potassium intoxication was present in spite of polyuria. This was treated with hypertonic glucose, calcium and insulin[18]. The patient deteriorated rapidly and on the third day a Levin tube was inserted and enteral electrolyte therapy was begun. A dramatic clinical and chemical response ensued. The patient became completely edema free and all therapy was stopped. Within 30 days there was a progressive deterioration and follow-up was lost. In retrospect it was felt that this patient would have benefited from continued therapy. Other than the dramatic improvement associated with electrolytes definite interpretation of this case is difficult because the patient did have 48 hours of bed rest and protein restriction before the electrolyte regimen was instituted.

CASE 3. P.E. was a 29-year-old male with a 5-year history and laboratory data indicating progressive chronic glomerulonephritis. Hypertension was severe and the patient was experiencing signs and symptoms of uremia. No improvement was noted with protein and salt restriction but an excellent result ensued with combined electrolyte therapy. The patient discontinued therapy and then the patient's urea rose to 133 mg. per 100 cc. within 10 days. Reinstitution of therapy over the next 14 days seemed to be associated with another drop of blood urea to 28 mg. per 100 cc. The patient continued in good condition on this regimen for many months. He then voluntarily discontinued therapy and over the next 2 months the urea rose to above 250 mg. and the patient expired. No further therapy was attempted during this time and postmortem examination revealed far advanced chronic glomerulonephritis.

CASE 4. R.P. who had advanced chronic glomerulonephritis and hypertension also had a 5-year history and laboratory data compatible with the disease. His course was almost identical to patient P.E. and cessation of therapy resulted in deterioration. Using this patient as his own control another good chemical and clinical result was obtained but the patient expired from a secondary infection while off electrolyte therapy.

CASE 5: J.M., known to have chronic glomerulonephritis for 5 years, suddenly developed increased microscopic hematuria, an elevated sedimentation rate and marked edema of the legs and face following an upper respiratory infection. After baseline data electrolyte therapy was begun because of a progression of uremia. A severe diastolic hypertension occurred over the next 7-day period. Medication was discontinued but bed rest, protein restriction and salt restriction were continued until the urinary findings and sedimentation rate returned to the previous levels. At this time the diastolic pressure returned to baseline level and electrolyte therapy was again begun. Then no hypertension resulted and it was felt that the earlier hypertension was directly related to the activity in the kidney lesion rather than to the administration of sodium. This patient was maintained on therapy for many months although he did not improve to the point of returning to work. The patient expired within about a year but did not receive electrolyte therapy within the last 2 months of his illness.

CASE 6. S.G. also was a known chronic glomerulonephritic of 5-years' duration. Although clinical improvement lasted only several months in this patient it was of interest that he received intravenous hypertonic sodium lactate 3 hours after an episode of acute pulmonary edema precipitated by a transfusion of packed blood cells. Initially an excellent response was obtained but the kidney lesion appeared to be progressive and the clinical picture of malignant hypertension ensued. Further unfavorable reactions from transfusion were believed to have been prevented by the administration of 40 to 80 cc. of one molar sodium lactate before and after each infusion of packed cells thereafter.

CASE 7. T.D. had known chronic glomerulonephritis for 5 years and was experiencing severe signs and symptoms of this disease. Before electrolyte therapy his glomerular filtration rate was reduced to 5 cc. per minute (inulin) and his Tmpah was reduced to 5 mg. per minute. Twenty-one days baseline data with protein restriction and forced calories failed to benefit this patient. With a single injection of sodium lactate (S.I.: Table 1) there was a drop in the blood urea nitrogen which lasted for 7 days. Thirty days more of protein restriction was carried out with a gradual rise in the blood urea nitrogen. When this rose to previous levels he was begun on oral electrolyte therapy and was able to return to work within a matter of weeks. He lived approximately 9 months and postmortem examination revealed far advanced chronic glomerulonephritis.

CASE 8. L.S. was admitted in a moribund condition. Severe acidosis and dehydration were present. After diabetic acidosis was excluded therapy was necessarily begun after about 30 hours of water hydration. The patient had an excellent clinical and chemical response. This case was initially difficult to interpret since all other measures of therapy were not tried. As the patient paid little attention to medical advice she discontinued electrolyte therapy on three occasions. Several weeks after each incident she was hospitalized for severe uremia and on each occasion combined electrolyte therapy was associated with improvement. Her existing hypertension apparently was not aggravated by sodium therapy and the patient died after 2 years from a cerebrovascular accident having received no electrolyte therapy for 3 months preceding the terminal event. Postmortem examination revealed far advanced chronic nephritis.

CASE 9. A.H. had acute nephritis as a child and 5 episodes of severe preeclampsia with pregnancies. Bilateral renal calculi were present and following an operation for possible obstruction on the left she became severely uremic. Excellent chemical and clinical results ensued and in spite of calcium therapy and an alkaline urine repeated pyelograms showed no increase in stone formation[48]. Maintenance therapy and follow-up have now been continued 20 months.

CASE 10. F.G. with chronic nephritis promptly went into shock and developed a febrile reaction following the administration of sodium lactate. (This was a special preparation not commercially available and is not to be confused with the recommended and repeatedly used Eli Lilly commercial preparation.) It was felt that this represented a pyrogenic reaction and the patient was unable to maintain her blood pressure for approximately 72 hours. During this period she was psychotic. Emergency treatment consisted of norepinephrine and plasma. After this episode she was placed on oral sodium lactate

and although chemical changes ensued little clinical benefit was obtained. At necropsy the patient had far advanced chronic glomerulonephritis.

CASE 11. G.S. was clinically terminal after having been exposed to most forms of treatment. He had 4 plus edema and failed to respond to mercurials, digitalis, and xanthines. With the onset of electrolyte therapy he sustained a 50 lb. weight loss as well as a dramatic chemical and clinical response. For the past 20 months this man has been on continuous therapy and is at present able to work daily.

CHRONIC PYELONEPHRITIS. CASE 12. H.D. was comatose and showed a progressive rise in his blood urea nitrogen in spite of 2 weeks' therapy with isotonic fluid replacement. Immediately on the institution of combined electrolyte therapy the urea nitrogen fell 65 mg. per 100 cc. in the next 24 hours. This drop continued and when clinically and chemically stabilized the patient had a compensated urea clearance of 6% normal with a total phenolsulfonphthalein of 2%. During the next 27 months this man sustained a 45 lb. nutritional weight gain and spontaneously corrected his anemia. The urea clearance has risen to 15% of normal and the phenolsulfonphthalein to 17% of total excretion. A recent intravenous pyelogram revealed no dye excretion in 75 minutes.

CASE 13. W.W. was an elderly man who was thought to be a typical picture of cerebral anoxia postoperatively. Although his azotemia was not severe this man was subjected to therapy and had a marked clearing of his mental condition. He was maintained on therapy for several months and it was then discontinued. Several days following withdrawal of therapy he went into a cycle of nausea and vomiting and became uremic. Therapy was instituted and the patient improved dramatically. He was then followed for 20 months but because of a progressive stricture in the esophagus, failing nutrition and discontinuance of medication took place. Following a vigorous insertion of a Levin tube the patient became comatose and expired. Necropsy revealed chronic pyelonephritis.

CASE 14. R.F., a 74-year-old white male, was admitted to the hospital with a past history of chronic pyelonephritis of 2-years' duration which caused complete incapacitation. The present hospital admission was for removal of a large bladder calculi. Five days following the suprapubic removal of a stone, the patient became comatose. This was probably related to a 24-hour period of immediate postoperative shock. Edema was 2 plus generalized and the patient was treated during the 5-day period for cardiac decompensation. Acidosis and twitching were prominent. The patient was then begun on a modified electrolyte regimen and received several small doses of hypertonic sodium chloride in addition to the sodium lactate. His response was good and the patient was completely rehabilitated for over a year on continuous therapy. The patient eventually died of secondary infection and necropsy revealed far advanced chronic pyelonephritis.

CASE 15. S.S. had a total cystectomy 3 years previously. He had one functioning kidney with a cutaneous ureterostomy. The patient became uremic and was admitted to the hospital in a moribund state. He responded well to therapy and was maintained as an outpatient for over 6 months. An overwhelming secondary infection in his opposite nonfunctioning kidney caused the patient's death. It is interesting that on one occasion, the patient was inadvertently given 400 mEq. of sodium lactate as a 50% solution and with one kidney was able to clear an equivalent amount within a 24-hour period.

POLYCYSTIC KIDNEY DISEASE. CASE 16. A.H. was known to have had advanced polycystic disease for 2 years previous to oral sodium lactate. He had been maintained during this time with 3 infusions of 1000 cc. of 1/6 molar sodium lactate and 500 cc. of blood each week. On oral therapy the patient was completely rehabilitated and returned to work. This patient had a very good 6 months but he was admitted to the hospital terminally because of psychosis which was supposed to be uremic in origin. His course at this time was rapidly downhill and further therapy was of no avail. He had discontinued therapy approximately 10 days before the final admission. At necropsy this patient's kidneys weighed 4000 gm. each.

CASE 17. M.Y. was admitted to the hospital for the 17th time in 16 years for polycystic kidney disease. For the first 2 weeks her course was rapidly downhill until she became moribund. During this time she received routine fluid therapy including 1/6 molar sodium lactate with no response. Upon institution of combined electrolyte regimen this patient had a dramatic response. She, too, is one of the cases in which small amounts of hypertonic sodium chloride were administered because of a rapid fall in the serum chloride level. In the compensated picture, this patient's urea clearance was 4% of normal and she had a total phenolsulfon-

phthalein excretion of 2%. This patient has now been rehabilitated for 27 months and has sustained 42 lbs. nutritional weight gain. Her kidney function tests have not improved. Her anemia has been well controlled, with cobalt chloride, 100 mg. daily.

HYDRONEPHROSIS. CASE 18. E.S. was a 31-year-old male with a hypoplastic kidney on the right and a stricture of the ureter on the left with hydronephrosis. Following a ureteral dilatation the patient developed acute uremia. It was interesting that during the period of progressive uremia the fluid intake was 6 liters daily and the output was 5 liters. The urea had been above 110 mg. per 100 cc. for a week and was rising when electrolyte therapy was begun. A dramatic improvement resulted and the patient was then taken off therapy, as kidney function tests were not severely depressed.

CASE 19. W.S. another case of postobstructive uremia, had adequate drainage for a period of a week, infection controlled and adequate hydration. His condition was too poor clinically to contemplate surgery. He was, therefore, started on the electrolyte regime preoperatively and following prostatectomy was kept on sodium lactate. He had an uneventful recovery and therapy was then discontinued.

CASE 20. J.C. represents a case of postobstructive uremia who had had adequate drainage, control of the infection and adequate hydration for over a month. Clinically, he became terminal and was begun on intravenous sodium lactate with a rapid favorable response.

Although favorable chemical changes resulted with this therapy in the initial 20 cases, the brief clinical remarks are compatible with Salvesen's findings that: a) alkali therapy should be used in all cases of uremia and acidosis when other measures fail to benefit the patient since a certain percentage of treated cases will have their life expectancy improved, and b) patients with kidney disorders other than chronic glomerulonephritis tend to do better with alkali therapy.

Discussion. Although the administration of sodium[19,54] and potassium[20,55] in advanced renal disease may frequently be inadvisable, their combined use appeared beneficial in many of the first series of cases studied. The physiological mechanisms involved are not clearly understood but certain definite chemical changes were seen, and usually these were accompanied by some degree of clinical improvement. With the administration of hypertonic sodium lactate and calcium lactate and in certain cases potassium as acetate or chloride, a fall in the blood urea nitrogen level was noted. This at times was quite marked. From the available data the fate of the blood urea nitrogen may not always be accounted for by an increase of urea in the urine. Delay in the formation of urea nitrogen or an actual metabolism of this substance within the tissues may occur.

With intensive alkali therapy a rapid rise in the CO_2-combining power was observed. This was caused by a conversion of lactate to bicarbonate. Complete data for analyses of the structure of the extracellular fluid were available in 18 cases. Of these, 8 cases before treatment had a CO_2-combining power below 8 mEq./L., while a total of 14 of the 18 cases showed CO_2-combining power below 20 mEq./L. These initial values are difficult to interpret since most of the cases were previously subjected to routine therapy and this at times included 1/6 molar sodium lactate. With one molar sodium lactate, however, 9 cases showed a rise in the CO_2-combining power to above 35 mEq./L. and, of these, 4 cases rose above 50 mEq./L. Under these altered circumstances with added calcium no tetany occurred. Although blood pH determinations were not available before treatment in this series, 10 cases which had been maintained on continuous therapy for 6 to 12 months showed a blood pH of 7.42. The effect of lactate may be solely the provision of bicarbonate. It is known, however, that lactate has a specific effect on the renal

tubular transport[10,26] system. It has a definite place in the Krebs cycle as well as being a source of energy for the liver[53]. The fact that lactate is converted to bicarbonate by cellular process may be of importance.

The reciprocal fall in the serum chloride level was probably due to the added bicarbonate but the expected chloruresis did not always occur. Fourteen of the 18 cases before treatment displayed a serum chloride level above 100 mEq./L. and, of these, 5 were above 110 mEq./L. In only one instance before treatment was the serum chloride value below 90 mEq./L. All 18 cases showed a drop in the serum chloride level with the administration of sodium lactate. Eight of these cases showed a fall in values for serum chloride below 80 mEq./L. and three of these fell to below 65 mEq./L. Since clinical improvement was apparent no attempt was made to restore the extracellular chloride except early in the series when 3 cases received a hypertonic sodium chloride-lactate solution (M.Y., R.F., S.S.). Several patients when allowed food showed an increasing serum chloride value indicating an inability to handle chloride. Paralleling this there was a rise in the blood urea nitrogen, but by increasing the dose of sodium lactate, this change could be reversed. The role of chloride in renal disease is obscure but early in the century Widal made the observation that when patients with renal disease could or could not excrete chloride the prognosis was thereby improved or worsened[38].

The serum sodium values were not used as a guide to therapy. In the 18 cases it was found that there was only one low and one high value before treatment (the rest being within the range of normal 135 to 141 mEq./L.) On sodium therapy there was little change in this value except in 2 instances when the serum sodium rose to above normal limits while on therapy. This was considered to be consistent with the relative water deficit and the fluid intake was increased with the subsequent fall in the serum sodium value.

The serum potassium in 18 cases were found to be in the range reported by Kolff[23]. Three low values and one high value were encountered. The other fourteen levels were normal. Potassium therapy was only used if the serum value was low or normal in face of good circulation and adequate urine output. With adequate calories, sodium lactate and calcium therapy all cases showed a drop in serum potassium values if supplementary potassium was not added. Potassium was not given in all cases and was administered only intermittently since with improved nutrition dietary potassium of 40 to 95 mEq. daily appeared to be adequate. Should the serum potassium not be sustained in a case with proper nutrition then potassium was added orally. The serum level for potassium was followed very carefully and in most cases receiving added potassium the cells apparently seemed to soon become saturated and the serum potassium value would become elevated, necessitating the discontinuance of the extra potassium. The ability of the kidney to excrete or secrete potassium[2,29,41] did not improve to the same extent as it did for clearing sodium, and early in the therapy several cases showed large retention of potassium. The effects of replacing a cell deficit of potassium are not understood and it has been suggested that potassium facilitates an excretion of sodium[39].

Urinary sodium concentration on baseline data showed low values in most cases, these being in the range of 7 to 25 mEq./L. in 24-hour samples. Total sodium excretion during the base-

line period was somewhat difficult to interpret since the majority of cases had been on varying degrees of sodium restriction and urine outputs varied. The low values may have reflected a conservative mechanism for sodium[35,40]. One case of polycystic disease (Case 16) on an unlimited diet excreted 90 mEq./L. of sodium. From these data and the clinical status it was felt that none of the cases was of the classical sodium or salt-losing nephritic type. During sodium therapy, most of the present series of cases showed a varying degree of retention of this ion, and this at times was of considerable magnitude (1000 mEq./L. in 8 days). In spite of the sodium retention no patient developed acute pulmonary edema, marked peripheral edema, or an increasing hypertension that could be related to sodium ingestion. Patients 1, 2 and 11 all lost edema fluid while receiving sodium as lactate. In Cases 2 and 11 there was an increased urinary volume while in Case 1 there was no increase in urine output but a retention of sodium occurred during the disappearance of edema fluid. With continued sodium lactate therapy, the sodium concentration of the urine rose slowly until it approached almost normal levels in every case regardless of the type or degree of renal pathology. All cases studied were able to excrete sodium in the range of at least 100 mEq./L., when administered as sodium lactate. This indicates perhaps, that the excretion of sodium in chronic renal disease may be intimately related to the anion with which it is administered.

When present the initial sodium retentions lasted from 3 to 10 days and gradually a much higher state of sodium equilibrium was approached than was seen during the baseline period. It was interesting in several cases with long follow-up data that after the period of sodium retention there was marked increased excretion of sodium in the urine, exceeding the quantities ingested at the time. This early base retention without evidence of edema or weight gain suggested the possibility of a cell cation deficit. The volume of distribution of hypertonic sodium lactate must have been much greater than the extracellular compartment as has been reported for sodium bicarbonate[49]. Perhaps the addition of sodium in an available form plus the increased bicarbonate excretion may have replaced or assisted in some of these functions ordinarily performed by the ammonia forming mechanism in the distal renal tubules.

Data on urinary ammonia were not available in this initial series. Urinary chlorides displayed no specific pattern. In most cases after therapy was begun levels remained at an essential equilibrium with the chloride intake of the diet.

From these data suggesting frequent sodium and potassium retention and from the data on tissue analysis where a potassium deficit was suspected, it cannot be absolutely stated that there is a cell cation deficit in advanced renal disease. Not only the natural history of disease but the presently accepted therapy of it would well produce a base deficit. Newburgh[34] pointed out the inherent dangers of low salt diet and predicted that should only a small negative excretion occur daily, eventual difficulties of considerable magnitude might ensue. As the disease progresses, nausea and vomiting are frequent, and the patient's state of nutrition and hydration may gradually decline over a period of months before treatment is instituted. With kidney damage and the associated inability to excrete acid metabolites with negative nitrogen balance, the necessity of drawing upon fixed body base has long

been recognized[1,16]. Thus, the acidosis in uremia may be not only a purely renal acidosis but also be associated with a deficit of body base. Therefore, the administration of large doses of alkaline sodium salts along with other electrolytes may be logical even in cases which are not typical sodium or potassium-losing nephritides. From the standpoint of calculated renal energy Newburgh[34] has shown that probably greater work is required of the distal tubules of the kidney for the formation of a urine hypotonic for sodium. Since the urinary concentration of sodium rose in all cases with sodium lactate a reduction in the expenditure of renal energy may have been a helpful factor in these cases where so little renal reserve is left. The use of a 20 gm. protein diet also decreased the expenditure of renal energy since less urea need be concentrated[5,22]. Then, too, this therapy may tend to support Platt's theory that the remaining nephrons can function at a supernormal capacity[40,41].

Side effects of this therapy are few and difficult to interpret. One case apparently had a pyrogen reaction and 2 patients became psychotic. This apparently was related to the sodium lactate but since psychoses occur frequently in uremia such a relationship is equivocal.

Indications and contraindications with expected chemical results from the regimen have been published elsewhere[31].

As this type of therapy has many inherent dangers, it must be stressed that it is still investigative in nature and should be attempted only when proper facilities are at the disposal of the physician.

Summary. 1. A combined electrolyte approach to the problem of uremia and acidosis has been presented. This consists of the administration of hypertonic sodium lactate, calcium salts, and occasionally potassium salts.

2. Twenty cases treated in this fashion have been presented. All except one showed varying degrees of improvement from slight to complete rehabilitation.

3. The most significant chemical changes encountered were a fall in the blood urea nitrogen, a rise in the CO_2-combining power, and a reciprocal drop in the extracellular chloride level.

4. It is felt that when usually available measures fail to benefit the uremic patient that this regimen may be of value.

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THE CARDIOVASCULAR AND RENAL HEMODYNAMIC RESPONSE TO THE ADMINISTRATION OF RESERPINE (SERPASIL)*

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Reserpine a pure alkaloid, which has been obtained from *Rauwolfia serpentina* and more recently has been chemically identified[16] has mild to moderate hypotensive activity[3]. Because of the relatively long delay period in the onset of action, the pharmacodynamics of this agent have been hard to evaluate. Nevertheless, the following report is an attempt to determine the cardiovascular and renal hemodynamic response to this drug following intravenous administration to laboratory animals and the renal hemodynamic response after both intravenous and oral administration to patients with hypertension.

Methods. CARDIAC OUTPUT STUDIES. Observations on cardiac output were made using the pulse contour method of Hamilton and Remington[1]. The dogs were anesthetized with 30 mg./kg. of pentobarbital or 15 mg./kg. of morphine and 10 mg./kg. of pentobarbital. Following suitable control observations reserpine (Serpasil)† was administered intravenously in doses of 3 or 4 mg. Observations on blood pressure, pulse rate, and cardiac output were then made every 15 minutes for the next 4 hours.

RENAL HEMODYNAMIC STUDIES. The acute renal hemodynamic response to intravenous reserpine (Serpasil) was observed on 10 dogs and 6 patients with hypertension. The effects of chronic administration (oral) were observed on 8 additional patients with hypertension.

Observations on dogs. The dogs were anesthetized with pentobarbital using 30 mg./kg. intravenously. Creatinine was used to measure glomerular filtration rate (GFR), and para-aminohippurate (PAH) was used to measure renal plasma flow. Mean blood pressure was measured by a damped mercury manometer connected through a manifold to an indwelling arterial needle. Observations on water and electrolyte excretions were made at the same time that the renal clearance studies were done. Except for minor modifications, the techniques and analytical methods have been previously described[2]. Following 3 suitable control periods (10 minutes each), 2 to 4 mg. of reserpine were administered intravenously. Two 10-minute clearance periods were collected immediately. Repeated observations (average of two 10-minute periods) were made 90 minutes, 2½ hours, and 4 hours after administering the reserpine. Then norepinephrine (1/100,000)

*Supported in part by grants from the Houston Heart Association and the Research Department of Ciba Pharmaceutical Products, Inc.

Presented before the New York Academy of Sciences, February 5, 1954.

†Supplied by Ciba Pharmaceutical Products, Inc.

was infused intravenously at a rate of 3 to 5 cc./minute. Observations were then made for 2 successive 10-minute collection periods.

Clinical studies. Differential renal function studies were done on 6 hypertensive patients who received reserpine intravenously. At the same time observations were made on water and electrolyte excretion. After 3 successive 10-minute periods, 1 to 3 mg. of reserpine were administered intravenously in 100 cc. of 5% glucose in water over a 10 to 20-minute period. Inulin was used to determine glomerular filtration rate and para-aminohippurate was used to measure renal plasma flow. The plasma concentrations of sodium and potassium and the excretion rates of these electrolytes in the urine were determined using a Beckman flame photometer for analyses. Techniques and analytical methods used have previously been described[5]. Following the administration of reserpine the blood pressure was recorded every 10 minutes for the next 6 hours. After a definite reduction in blood pressure was observed and when it appeared that further reduction probably would not occur, observations on renal plasma flow, glomerular filtration rate and the excretion of water and electrolytes were again made. Two 10-minute collection periods were obtained, the average of which is designated as D_1 in Table 3A and 3B. After a delay period of 35 minutes or more, 2 additional collection periods were made, the average of which is designated as D_2.

Observations on renal hemodynamics and electrolyte excretion were made on 8 patients with hypertension who received 3 to 6 mg. of reserpine* orally each day for 3 months. Control observations consisted of three 10-minute collection periods. Similar collection periods were obtained after the 3-month period of drug administration. The techniques used were previously described[5].

Results. LABORATORY OBSERVATIONS. *Cardiovascular Hemodynamics.* After a variable period of one to 2 hours the blood pressure usually decreased moderately and the reduction in blood pressure lasted from 2 to 5 hours. Associated with the reduction in blood pressure the cardiac output was quite variable, occasionally decreasing slightly. Generally speaking, however, the drug did not appear to have a consistent effect on cardiac output and the reduction in blood pressure which usually occurred was due primarily to a decrease in peripheral resistance. About one-fourth of the animals failed to show a significant reduction in blood pressure.

In most instances there was an immediate drop and return to above control levels in blood pressure on injection of reserpine (Fig. 2) probably due to the effect of the vehicle, polyethylene glycol. This was tested in several additional control dogs by several injections of polyethylene glycol in amounts equal to that of an injection of reserpine. Usually an immediate reduction in blood pressure occurred with a rebound to and above control levels within a few minutes.

Renal Hemodynamic Studies. All of the dogs in this study showed a reduction in blood pressure from 60 to 90 minutes after administration of the drug. However, by the 4-hour post-drug period the blood pressure usually returned toward or exceeded the control blood pressure. The reduction in blood pressure was not associated with significant alterations in glomerular filtration rate or in renal plasma flow. However, 3 to 4 hours after administration of the drug, the renal plasma flow was reduced in some of the animals. This was apparently not due to the reduction in blood pressure in these animals since the blood pressure was usually approaching or had already returned to control levels. There was no consistent effect on sodium and potassium excretion or in the concentrations of these electrolytes in the plasma (Table 1B).

Following reserpine, the renal hemodynamic response to norepinephrine was similar to animals which had not previously received reserpine[4]. As the

*Supplied through the courtesy of Ciba Pharmaceutical Products, Inc., Chilcott-Warner, Inc., and the Riker Laboratories, Inc.

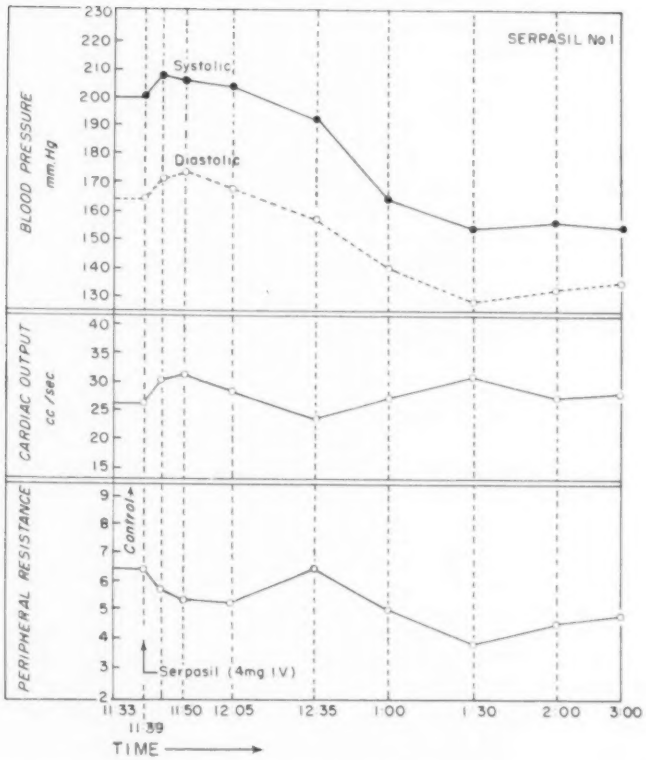

Fig. 1.—Typical response to reserpine (4 mg.). Following administration of the drug the blood pressure was variable (increased in this instance [Fig. 1] and then returned to control level) for approximately the first hour. Then both the systolic and diastolic pressures usually decreased below control levels for at least 2 to 5 hours. The reduction in blood pressure was associated with a reduction in peripheral vascular resistance. The cardiac output was quite variable. Sometimes it was above the control observations, more frequently it was below the control, but in general it did not deviate from the control value to any great extent.

TABLE 1A.—THE RENAL HEMODYNAMIC RESPONSE TO RESERPINE

Dog Number	*Mean Blood Pressure mm. Hg*					*Glomerular Filtration Rate cc./min.*					*Renal Plasma Flow cc./min.*				
	C	D_1	D_2	D_3	D_4	*C*	D_1	D_2	D_3	D_4	*C*	D_1	D_2	D_3	D_4
1.	162	148	137	151	179	33	40	43	38	37	90	125	130	87	74
2.	131	133	—	109	120	41	40	—	34	34	150	157	—	93	83
3.	136	134	111	98	123	51	51	44	44	44	158	143	137	133	90
4.	170	172	159	181	188	39	43	46	43	45	109	127	129	94	89
5.	133	125	83	103	133	43	48	57	50	60	128	174	182	132	154
6.	152	148	119	131	128	51	55	43	47	50	187	208	159	160	198
7.	189	170	122	135	153	25	—	36	37	38	80	—	99	81	77
8.	136	133	114	122	114	127	99	113	97	110	333	284	282	223	243
9.	130	137	73	98	120	63	62	54	51	56	216	220	185	156	171
10.	180	165	139	146	150	45	45	46	47	47	180	185	159	128	127
Mean	152	147	117	127	141	52	54	54	49	52	163	180	162	129	131

C—Control observations (average of three ten-minute periods).
D_1—Observations immediately after the administration of reserpine (average of three ten-minute periods).
D_2—Observations ninety minutes after the administration of reserpine (average of two ten-minute periods).
D_3—Observations two and one-half hours after reserpine (average of two ten-minute periods).

blood pressure increased, renal blood flow was depressed. This was reflected in a sharp increase in renal vascular resistance (Table 2A). Norepinephrine did not produce a consistent effect on electrolyte excretion except in those instances where glomerular filtration rate was markedly depressed. Then the excretion of water and electrolytes was also depressed (Table 2B).

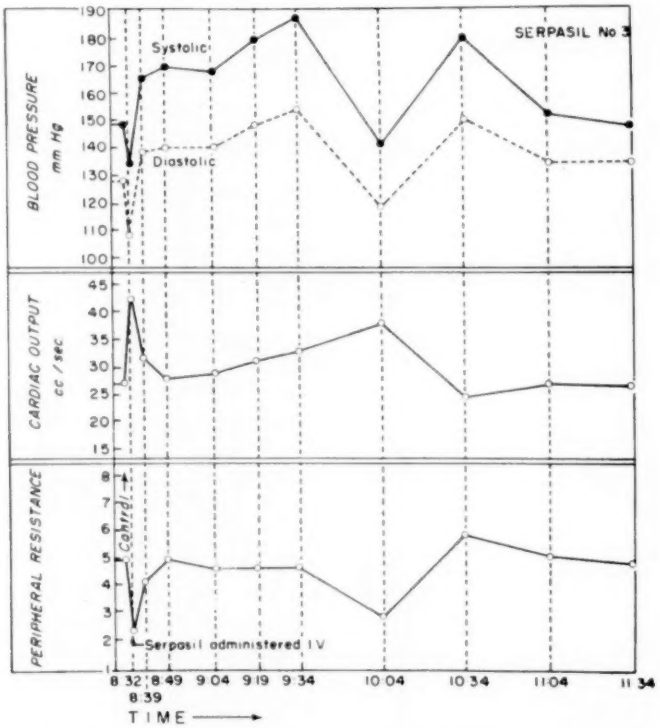

Fig. 2.—Atypical cardiovascular response to reserpine which was sometimes observed. The cardiovascular hemodynamics appeared quite unstable but there was no consistently significant effect on blood pressure or on cardiac output. The initial and transient reduction in blood pressure is probably due to the vehicle, polyethylene glycol.

SERPASIL) ADMINISTERED INTRAVENOUSLY TO DOGS

Renal Blood Flow cc./min.					*Renal Vascular Resistance**					*Hematocrit*				
C	D_1	D_2	D_3	D_4	*C*	D_1	D_2	D_3	D_4	*C*	D_1	D_2	D_3	*D*
158	219	210	140	117	1.03	.68	.65	1.09	1.53	43	43	38	38	37
242	253	—	152	134	.54	.53	—	.72	.90	38	38	—	39	38
272	247	217	211	137	.50	.54	.51	.46	.90	42	42	37	37	35
185	215	226	165	153	.92	.80	.70	1.10	1.23	41	41	43	43	42
229	311	325	220	257	.58	.40	.26	.47	.52	44	44	44	40	40
288	335	284	266	336	.53	.44	.42	.44	.38	35	38	44	46	41
157	—	183	150	151	1.20	—	.67	.90	1.01	49	49	46	46	49
584	498	495	391	426	.23	.28	.23	.31	.27	43	43	43	43	43
424	440	370	312	323	.31	.31	.20	.31	.37	49	50	50	50	47
265	280	245	267	265	.68	.59	.57	.55	.57	32	34	35	52	52
280	311	284	230	230	.65	.51	.47	.64	.77	42	42	42	43	42

D_4—Obervations four hours after the administration of reserpine (average of two ten-minute periods).

* Renal Vascular Resistance = $\frac{\text{Mean Blood Pressure.}}{\text{Renal Blood Flow}}$

TABLE 1B.—THE EFFECT OF RESERPINE ON WATER AND ELECTROLYTE EXCRETION

Dog Number	Urine Volume cc./min.				Plasma Concentration								Urine Excretion											
					Sodium mEq./L.				Potassium mEq./L.				Sodium μEq./min.				Potassium μEq./min.			
	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3
1.	5.4	5.3	7.1	6.5	152	156	156	159	3.6	3.6	3.6	3.1	56	394	470	395	34	33	74	56
2.	1.2	1.7		1.4	149	149	—	146	3.1	3.2	—	3.4	82	69	—	59	39	33	—	39
3.	1.6	3.9	2.4	1.6	138	138	146	146	3.7	3.5	2.9	3.6	155	258	85	58	39	47	44	40
4.	1.0	7.6	2.4	1.5	147	138	146	155	3.5	3.1	2.6	3.1	432	482	287	216	55	41	59	61
5.	0.6	3.6	2.1	0.9	133	146	146	147	3.3	3.1	2.6	3.0	232	289	280	230	54	32	50	68
6.	0.7	3.6	2.1	1.7	140	155	155	155	3.4	3.5	2.6	3.3	267	460	553	289	54	55	59	84
7.	1.9	2.0	3.1	1.9	131	133	138	139	3.0	3.3	2.4	3.3	242	260	547	295	44	45	55	82
8.	0.8	2.6	1.6	0.7	140	145	131	131	2.6	3.3	2.2	3.3	109	370	740	446	14	15	45	25
9.	0.8	1.4	1.7	2.4	140	145	145	148	2.6	2.8	2.2	2.1	64	122	328	148	18	39	26	24
10.													40	48	53	46	20	37		27
Mean	2.1	3.2	3.1	2.7	143	146	144	145	3.1	2.7	2.8	2.9	168	192	184	129	26	36	43	57
								145				2.9				174				47

C, D_1, D_2, D_3—See Table 1A for key to abbreviations.

CLINICAL OBSERVATIONS. The results obtained after intravenous administration of reserpine to 6 patients with hypertension are presented in Tables 3A and 3B. All but one of the patients showed some reduction in blood pressure. Usually this was not marked. However, there was one exception (patient 5, D.D.) in whom the blood pressure dropped excessively and it was necessary to administer norepinephrine for about one hour before the blood pressure was stabilized at an adequate level without the support of vasoconstrictor drugs. During the severe hypotensive phase the patient was irrational, disoriented, and lethargic. In these patients the shortest delay period before the onset of blood pressure reduction was one hour and the average for the group was one hour and 32 minutes. The maximum reduction in blood pressure occurred on the average about 3 hours after the reserpine was administered. The first post-drug collection period (D_1) was made (on the average) about 3 hours after the drug was administered and the second post-drug observations (D_2) were made about 4 hours after the reserpine was administered.

There were no consistent effects on renal hemodynamics. In a few of the patients glomerular filtration rate was somewhat reduced but this was inconstant and of little consequence. Renal blood flow increased in one patient, was depressed in 2 and was not altered significantly in the remaining 3 patients. Side reactions of nasal congestion and somnolence were quite frequently observed (Table 3A). The excretion rates for sodium and potassium before and after intravenous administration of reserpine are summarized in Table 3B. There was very little effect on this function and no alteration of the concentration of these electrolytes in the plasma.

The blood pressure and renal hemodynamic response to the oral administration of reserpine (Serpasil) for 3

TABLE 2A.—EFFECT OF NOREPINEPHRINE ADMINISTRATION BY CONTINUOUS INTRAVENOUS INFUSION FOLLOWING THE PREVIOUS ADMINISTRATION OF RESERPINE

Dog Number	Mean Blood Pressure mm. Hg				Glomerular Filtration Rate cc./min.				Renal Plasma Flow cc./min.				Renal Blood Flow cc./min.				Renal Vascular Resistance*				Hematocrit			
	C	D_4	N_1	N_2	C	D_4	N_1	N_2	C	D_4	N_1	N_2	C	D_4	N_1	N_2	C	D_4	N_1	N_2	C	D_4	N	N_2
2.	131	120	149	178	41	34	38	42	150	83	89	90	242	136	144	143	.54	.88	1.03	1.23	38	39	38	38
5.	133	133	157	173	43	60	49	17	128	154	135	43	229	257	225	72	.58	.52	.70	2.40	44	40	40	40
6.	152	128	186	175	51	50	37	49	187	198	119	142	288	336	220	263	.53	.38	.85	.67	35	41	46	46
7.	189	153	256	260	25	38	26	1	80	77	48	—	157	151	94	—	1.20	1.01	2.72	—	49	49	49	49
9.	130	120	167	195	63	56	67	64	216	171	157	143	424	323	314	286	.31	.37	.53	.68	49	47	50	50
10.	180	150	202	200	45	47	38	44	180	127	102	97	273	265	268	255	.66	.57	.75	.78	34	52	62	62
Mean	153	134	186	197	45	48	43	36	157	135	108	103	269	245	211	204	.64	.62	1.10	1.15	42	45	48	48

C—Control (average of three ten-minute periods).
D_4—Observations (average of two periods) made four hours after the administration of Reserpine.
N_1 and N_2—Observations (successive ten-minute periods) made during the continuous infusion of norepinephrine.
* See Table 1A.

TABLE 2B.—THE EFFECT OF NOREPINEPHRINE FOLLOWING RESERPINE ON WATER AND ELECTROLYTE EXCRETION

Dog Number	Urine Volume cc./min.				Plasma Concentration (mEq./L.) Sodium				Plasma Concentration (mEq./L.) Potassium				Urine Excretion Rate (μEq./min.) Sodium				Urine Excretion Rate (μEq./min.) Potassium			
	C	D_4	N_1	N_2	C	D_4	N_1	N_2	C	D_4	N_1	N_2	C	D_4	N_1	N_2	C	D_4	N_1	N_2
2.	1.2	3.7	4.9	4.8	149	146	140	140	3.1	3.8	3.8	3.6	82	177	81	86	29	39	54	57
5.	0.8	3.3	3.6	0.8	143	147	147	152	3.3	3.3	3.3	3.8	72	389	400	83	25	111	122	31
6.	0.7	3.6	1.4	1.0	150	165	165	165	3.4	3.3	2.7	2.7	97	174	93	66	24	48	32	28
7.	0.7	3.2	1.4	0.2	140	138	138	138	2.5	1.7	1.7	1.7	23	68	24	4	4	28	13	1
9.	0.8	2.4	6.2	7.7	134	134	131	131	2.8	2.1	2.1	2.1	64	15	43	59	18	24	30	30
10.	1.7	3.2	2.2	2.0	145	133	135	135	2.3	2.4	2.3	2.3	48	46	38	38	27	27	21	21
Mean	1.0	3.2	3.3	2.8	144	144	143	144	2.9	2.8	2.7	2.7	64	145	113	56	21	46	45	28

C, D_4, N_1 and N_2—See Table 2A.

TABLE 3A.—ACUTE RENAL HEMODYNAMIC RESPONSE TO THE INTRAVENOUS ADMINISTRATION OF RESERPINE IN PATIENTS WITH HYPERTENSION

	Mean Blood Pressure mm. Hg			*Glomerular Filtration Rate cc./min.*			*Renal Blood Flow* cc./min.*			*Renal Plasma Flow cc./min.*			*Renal Vascular Resistance‡*			*Hematocrit*			*Pulse Rate*			
Patient	*C*	D_1	D_2	*C*	D_1	D_2	*C*	D_1	D_2	*C*	D_1	D_2	*C*	D_1	D_2	*C*	D_1	D_2	*C*	D_1	D_2	*Side Reactions*
1. W.B.	142	106	107	95	88	81	785	1078	1319	471	679	752	.18	.10	.08	40	37	43	64	66	64	Nasal congestion somnolence
2. W.S.	184	151	153	61	57	60	806	662	614	419	351	356	.23	.23	.25	48	47	42	66	73	74	Stomach cramps
3. O.H.	158	148	144	85	66	68	676	608	619	419	365	384	.23	.24	.23	38	40	38	73	78	88	Nausea
4. W.T.	121	119	124	77	68	66	733	674	647	469	411	401	.17	.18	.19	36	39	38	69	76	74	None
5. D.D.	146	115†	126†	94	79	83	769	639	573	446	364	321	.19	.18	.22	42	43	44	56	72	80	See footnote
6. M.D.	126	113	117	61	92	89	560	569	558	325	350	329	.23	.20	.21	42	42	41	60	48	48	Nasal congestion, somnolence
Mean	146	125	129	79	75	75	722	705	722	425	417	424	.21	.19	.20	41	41	41	65	69	71	

* Renal Blood Flow = Renal Plasma Flow/1-Hematocrit.

‡ Renal Vascular Resistance = $\frac{\text{Mean Blood Pressure.}}{\text{Renal Blood Flow}}$

† Blood pressure maintained at this level with norepinephrine due to excessive reduction following Serpasil to 70 mm. Hg systolic. Hypotension was accompanied by restlessness, cold sweats, air hunger, drowsiness, and wheezing.

C—Control

D_1—Observations made at anticipated maximum reduction in blood pressure (average of two ten-minute periods).

D_2—Average of two ten-minute collection periods taken 50 to 70 minutes after D_1.

TABLE 3B.—THE EFFECT OF INTRAVENOUS RESERPINE ON WATER AND ELECTROLYTE EXCRETION IN PATIENTS WITH HYPERTENSION

	Plasma Concentration mEq./L.						*Urine Excretion Rate μEq./min.*									*Renal Clearance Done Hours After Reserpine*	
	Sodium			*Potassium*			*Sodium*			*Potassium*							
Patient	*C*	D_1	D_2	*C*	D_1	D_2	*C*	D_1	D_2	*C*	D_1	D_2	*Dose mg.*	*Onset of B.P. Reduction in Hours*	*Maximum B.P. Reduction in Hours*	D_1	D_2
1. W.B.	138	139	139	4.92	4.17	4.17	134	120	132	60	71	74	2.0	1:00	3:00	3:00	3:50
2. W.S.	134	138	138	5.07	5.07	5.07	281	87	61	43	27	29	2.0	2:50	3:00	3:30	4:20
3. O.H.	139	144	140	4.54	3.76	3.43	428	206	404	65	57	79	1.0	1:25	2:50	1:50	2:50
4. W.T.	128	132	130	5.12	4.46	4.17	196	871	1055	16	29	32	2.0	—	—	5:00	5:50
5. D.D.	141	141	141	5.18	4.41	4.41	142	28	32	30	50	29	2.0	1:25	3:00	3:50	4:50
6. M.D.	140	135	135	4.72	3.89	3.92	129	42	37	47	54	56	3.0	1:00	2:50	2:50	3:25
Mean	137	138	137	4.93	4.29	4.20	218	226	287	44	48	50	2.0	1:32	2:56	3:18	4:11

C, D_1, and D_2—See Table 3A for key to abbreviations.

months is presented in Table 4A and the effect on electrolyte excretion in Table 4B. Six of the 8 patients thus studied showed a significant reduction in blood pressure. There was no evidence of depression in renal function or in the excretion of electrolytes. Plasma sodium and potassium concentrations were essentially unchanged after receiving reserpine for 3 months.

TABLE 4A.—RENAL HEMODYNAMIC RESPONSE TO THE ORAL ADMINISTRATION OF RESERPINE FOR THREE MONTHS

Patient No.	Mean Blood Pressure* mm.Hg		Glomerular Filtration Rate cc./min.		Renal Plasma Flow cc./min.		Hematocrit		Renal Blood Flow cc./min.		Renal Vascular Resistance**	
	C	D	C	D	C	D	C	D	C	D	C	D
1. L.B.	143	103	124	111	722	630	51	40	1473	1050	.10	.10
2. E.M.	169	120	91	88	657	682	53	39	1398	1118	.12	.11
3. J.J.	150	139	146	112	816	731	45	42	1484	1260	.10	.11
4. J.H.	165	130	112	119	434	655	38	38	700	1056	.24	.12
5. L.M.	124	98	109	80	704	754	39	41	1154	1278	.11	.08
6. L.B.	173	137	78	93	362	453	52	44	754	809	.23	.17
7. W.C.	147	147	115	114	539	466	44	40	963	777	.15	.19
8. D.D.	146	147	94	101	446	394	42	43	769	691	.19	.21
Mean	152	128	109	102	585	596	46	41	1087	1005	.16	.14

* Direct intra-arterial manometry.

** Renal Vascular Resistance = $\frac{\text{Mean Blood Pressure.}}{\text{Renal Blood Flow}}$

C—Control observations (average of three ten-minute periods).

D—Observations made (average of three ten-minute periods) three months after reserpine therapy started, administering 3 to 6 mg./day.

TABLE 4B.—THE EFFECT OF ORAL ADMINISTRATION OF RESERPINE FOR THREE MONTHS ON ELECTROLYTES

Patient	Urine Volume cc./min.		Plasma Concentration mEq./L.				Urine Excretion μEq./min.			
			Sodium		Potassium		Sodium		Potassium	
	C	D	C	D	C	D	C	D	C	D
1. L.B.	21.2	12.0	135	133	4.2	4.0	182	177	23	65
2. E.M.	10.4	12.4	142	132	4.6	3.7	294	272	51	26
3. J.J.	19.1	4.1	145	140	3.5	4.5	209	235	57	64
4. J.H.	6.9	10.8	140	138	5.1	5.6	301	355	49	53
5. L.M.	9.8	14.7	136	144	4.6	4.3	147	161	31	36
6. L.B.	6.3	4.7	145	144	5.0	4.2	229	231	48	35
7. W.C.	4.9	19.5	134	134	4.6	4.3	285	483	58	57
8. D.D.	5.9	6.5	141	137	4.4	4.9	142	400	30	44
Mean	10.6	10.6	140	138	4.5	4.4	224	289	43	48

C, D—See Table 4A.

Summary and Conclusions. Observations have been made on the cardiovascular and renal hemodynamic response to reserpine. The drug was administered intravenously to dogs and patients with hypertension and orally (for a period of 3 months) to patients with hypertension.

Following intravenous administration of the drug to dogs, cardiac output

was quite variable and was sometimes reduced during the period of blood pressure reduction. However, these alterations were of short duration and were usually of little consequence. Renal hemodynamics and electrolyte excretion rates were also not altered significantly after intravenous administration of reserpine to dogs.

When reserpine was administered to patients with hypertension, renal blood flow, glomerular filtration rates, and the renal excretion of water and electrolytes were not altered, either after intravenous administration or after oral administration for 3 months. There was no evidence of renal toxicity or depression of renal function. Reserpine is only moderately potent in its ability to reduce blood pressure, both after intravenous and chronic oral administration of the drug.

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ORTHOXINE-THEOPHYLLINE FOR THE RELIEF OF BRONCHIAL ASTHMA

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Aminophylline is one of the most useful drugs employed in the treatment of bronchial asthma. Chemically, it is a combination of theophylline (in various concentrations) with ethylene diamine. Theophylline, a member of the xanthine group, is the relatively insoluble, active agent, and ethylene diamine is added principally to increase its solubility. Thorough experimental and clinical trials with aminophylline in the last 15 years or so have proven its effectiveness in relieving bronchospasm, whether given rectally, intravenously, or by intramuscular injection. It has been shown to be less successful orally, because of limited dosage due to the production of nausea, and virtually ineffective by the aerosol route. Its action by these different routes has been quantitated in this laboratory, on the basis of its ability to protect asthmatics from their usual bronchospastic response to the injection or inhalation of histamine and methacholine[10].

A more recent agent to be used for the relief of bronchospasm is Orthoxine hydrochloride[8]. Orthoxine is related structurally to the commonly used sympathomimetic drugs, but it has very little pressor activity[1,2]. Animal studies have shown its dextro-isomer to have an anticholinergic action equal to, and an antihistaminic action thirty times as great as, that of ephedrine[3]. In clinical studies done in this laboratory, *racemic* Orthoxine, given intravenously, protected asthmatic subjects significantly well against the bronchospastic effects of histamine and methacholine, and was also effective against spontaneous attacks of acute bronchial asthma[9].

Orthoxine-theophylline replaces the pharmacologically inert ethylene diamine in aminophylline with the free base of Orthoxine, in an attempt to increase theophylline's effectiveness as well as its solubility. It is a definite chemical compound formed by the combination of unimolecular equivalents of its two ingredients in the presence of water. Containing 50.8% of theophylline by weight, it is highly stable and water soluble[4].

In animal studies, Orthoxine-theophylline was found to be a more potent bronchodilator than either

aminophylline or Orthoxine alone, suggesting that their effects are additive. Its toxicity and its stimulating effect on the central nervous system have been found to be no greater than that of aminophylline. Its coronary dilator effect has appeared superior[4].

Because of the favorable laboratory results reported above with Orthoxine-theophylline, we undertook to investigate this new compound on a clinical level. Determination of the blood levels of theophylline by various routes of administration, its effectiveness against spontaneous or induced bronchospasm, and its freedom from side effects were studied.

Methods. I. BLOOD LEVELS. The blood levels of theophylline that were produced by intravenous or rectal administration of Orthoxine-theophylline were compared with those obtained with aminophylline employing normal subjects. Doses of 500 mg. of aminophylline and 750 mg. of Orthoxine-theophylline were given. Each of these preparations contained 395 mg. of theophylline. Blood samples were collected before as a control and then 15, 30 minutes, 1, 2, and 7 hours after drug administration. The plasma concentration of theophylline in these samples was measured spectrophotometrically,* employing the method of Truit *et al.*[11].

II. EFFECTIVENESS AGAINST BRONCHOSPASM. The following studies were carried out.

A. The acute bronchodilator potency of Orthoxine-theophylline was measured by observing the effects of either 250 mg. by aerosol with the Vaponefrin nebulizer oxygen flow technique, or intravenous injection, or of 400 mg. orally, on the vital capacity and maximal breathing capacity of a number of asthmatic subjects during bronchospasm and in various stages of remission.

B. Effectiveness of Orthoxine-theophylline against severe asthma was evaluated first by the clinical response of patients (relief of wheezing and dyspnea) to the intravenous administration of a single dose of 250 to 500 mg. Second, those patients who required hospitalization because of severe and prolonged status asthmaticus were given Orthoxine-theophylline by continuous intravenous drip, 500 mg. in 1000 cc. of dextrose in water every 8 hours, for several days and observed for effect.

C. The effectiveness of Orthoxine-theophylline in protecting against induced bronchoconstriction was measured by the technique of "protection studies"[7]. This consists briefly of recording the vital capacity before and after the administration of a bronchospastic agent, histamine or methacholine intravenously, obtaining the maximum possible drop in vital capacity. The protecting drug is then administered and the bronchospastic agents given again. The percentage of protection subsequently afforded by the use of the protecting agent is thus determined. In this study, Orthoxine-theophylline (250 mg. in all but one instance) was administered by aerosol or intravenously to asthmatic subjects in remission.

D. The effectiveness of Orthoxine-theophylline in the long-term treatment of asthma was studied by giving it orally to asthmatics in incomplete remission, in a dose of 200 mg. 4 times a day over an average period of 6 weeks.

III. SIDE EFFECTS. Side effects following Orthoxine-theophylline administration were recorded.

Results. I. BLOOD LEVELS. The results of this study are graphically shown in Fig. 1. Patient A was given 750 mg. of Orthoxine-theophylline and patient B, 500 mg. of aminophylline, both intravenously. Each of these preparations contained 395 mg. of theophylline. The highest blood level of theophylline in A was 1.13 mg. per 100 cc. at 15 minutes, and the highest level in B was 0.76 mg., obtained in 30 minutes. Excellent levels persisted in both for 2 hours after injection. Patients C and D were given equivalent doses rectally of Orthoxine-theophylline and aminophylline respectively. The maximum blood level of theophylline obtained in patient C (Orthoxine-theophylline) was 0.33 mg. per 100 cc., obtained in the 30-minute sample. In patient D (aminophylline), a similar concentration was reached in 30 minutes, but

*We gratefully acknowledge our indebtedness to Drs. C. Woods and L. Burgin for collecting the blood samples, and to Miss Mildred Prestud of the Upjohn Company, Kalamazoo, Michigan, laboratories for making the theophylline determinations.

almost double this value or 0.63 mg., was noted at 2 hours.

II. EFFECTIVENESS AGAINST BRONCHOSPASM. A. *Effect of Orthoxine-theophylline on vital capacity and maximal breathing capacity of asthmatic patients*: 1. DURING EXACERBATION. Intravenous administration of a single dose of 250 mg. of Orthoxine-theophylline to 5 patients during acute asthmatic attacks produced an average rise in vital capacity from 1875 cc. to 2275 cc., and an average increase in maximal breathing capacity (M.B.C.) from 47.2 liters per minute to 58.1 liters per minute. Six inhalations of Neosuprel, a sympathomimetic bronchodilator[5], produced a further rise in vital capacity to 2725 cc. and in M.B.C. to 73.9 liters per minute (Figs. 2A and 2B). Aerosol administration of 250 mg. of Orthoxine-theophylline to one patient in an acute asthmatic attack produced a rise in vital capacity from 750 cc. to 1250 cc. Six inhalations of Neosuprel produced a further rise to 2500 cc.

2. DURING REMISSION. The effect of a single dose of Orthoxine-theophylline on vital capacity and M.B.C. of asthmatic patients in subjective remission was measured in 18 patients (Figs. 3 and 4). Seven patients were given 250 mg. of Orthoxine-theophylline intravenously, with a resultant average rise in vital capacity from 2258 cc. to 2792 cc., and in M.B.C. from 38 liters per minute to 63.6 liters. Neosuprel aerosols effected an additional increase in vital capacity of 150 cc. and in M.B.C. of 0.8 liters per minute.

Four patients in remission were given 250 mg. of Orthoxine-theophylline by aerosol. This was followed by an average rise in M.B.C. from 53.0 liters per minute to 63.0 liters. Vital capacity was measured in 2 patients, and rose with treatment from 2825 cc.

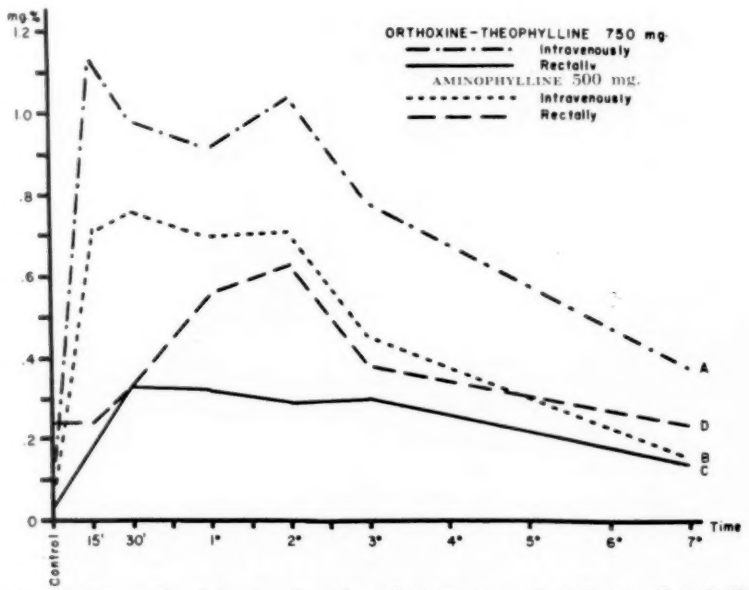

Fig. 1.—Theophylline—Blood levels after the administration of Orthoxine-theophylline (750 mg.) and aminophylline (500 mg.) rectally and intravenously.

to 3262 cc. Neosuprel aerosols produced a further rise in M.B.C. of 5.5 liters and in vital capacity, of 188 cc. Seven patients in subjective remission were given two tablets, or 400 mg., of Orthoxine-theophylline orally. Vital capacity was virtually unaffected, rising from 3443 cc. to a maximum average of 3450 cc. The M.B.C. of this same group, however, rose from an average of 65.5 liters per minute to 94.7 liters. Neosuprel aerosols produced

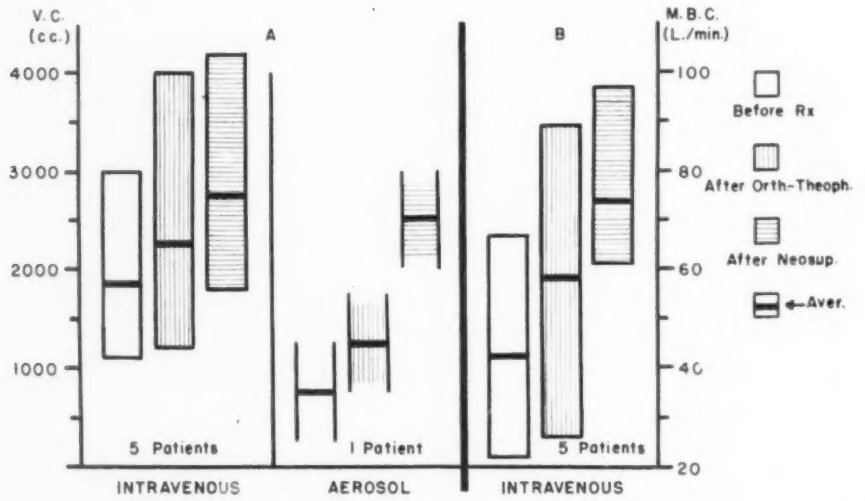

Fig. 2.—Changes in range and average of vital capacities (A) and maximal breathing capacities (B) after the administration of Orthoxine-theophylline (aer. 8 i.v.) and Neosuprel (aer.) in 11 acute bronchial asthmatic subjects.

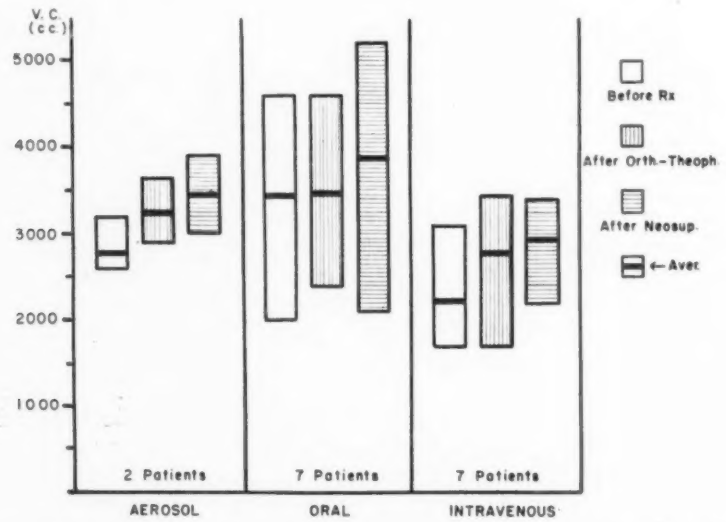

Fig. 3.—Changes in range and average of vital capacities after the administration of Orthoxine-theophylline (aer., p.o., 8 i.v.) and Neosuprel (aer.) in 16 symptom-free asthmatic subjects.

a further increase of 438 cc. in vital capacity, and of 26.8 liters per minute in M.B.C.

B. *Clinical effectiveness in severe asthma.* The clinical effect of intravenous Orthoxine-theophylline on the wheezing and dyspnea of the acute asthmatic attack was observed in 34 patients. Twenty patients were given 500 mg. of Orthoxine-theophylline by injection. Eighteen of the 20 had severe bronchospasm with 4+ wheezing prior to therapy. There was considerable immediate improvement in every case, all patients feeling and appearing less dyspneic. Two had 2+ wheezing, eleven had 1+ wheezing as a residuum, and 7 became completely clear. The results are listed in Table 1. Fifteen of the 20 patients complained of side effects, however, ranging from faintness and dizziness to sweating, nausea, and actual vomiting.

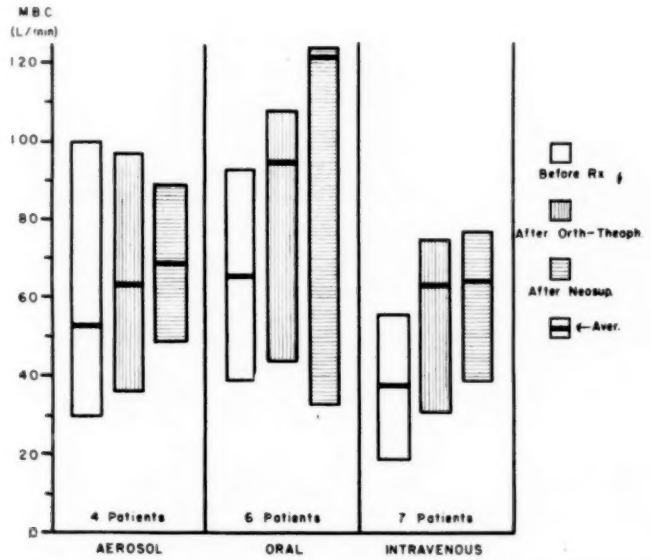

Fig. 4.—Changes in range and average of maximal breathing capacities after the administration of Orthoxine-theophylline (aer, p.o., 8 i.v.) and Neosuprel (aer.) in 17 symptom-free asthmatic subjects.

TABLE 1.—THE EFFECTS OF 500 MG. OF ORTHOXINE-THEOPHYLLINE INTRAVENOUSLY ON 20 PATIENTS WITH ACUTE BRONCHIAL ASTHMA

	Number of Patients		*Reactions*	
Degree of Wheezing	*Before Treatment*	*After Treatment*	*Type*	*Number*
4+	18	—	Faintness	2
3+	2	—	Sweating	3
2+	—	2	Nausea	11
1+	—	11	Vomiting	4
0	—	7	No Reaction	5

Consequently, 14 additional patients were given a small intravenous dose of Orthoxine-theophylline, ranging from 250 to 300 mg. There was again excellent clinical improvement, but with

fewer and milder side reactions, one patient feeling faint, and 3 experiencing slight nausea. These results are listed in Table 2.

Ten patients, who had been in severe status asthmaticus for several days requiring hospitalization, were given a slow intravenous drip of Orthoxine-theophylline, 0.5 gm. in 1000 cc. of 5%-dextrose in water every 8 hours for 3 or more days. There was a generally good response, and no side reactions were observed. Five of these patients had previously received aminophylline by slow drip for a period of 2 or three days and had not improved with it, suggesting that Orthoxine-theophylline was superior in these patients to aminophylline alone.

C. *Effectiveness against induced bronchoconstriction: Protection study technique.* Five patients were given histamine intravenously, preceded in 2 by Orthoxine-theophylline aerosol, and in 3 by Orthoxine-theophylline intravenously. Eight patients were given methacholine intravenously, preceded in 6 by aerosol Orthoxine-theophylline and in 2 by intravenous medication. All patients but one received 250 mg. of the drug. The results are listed in Table 3.

Intravenous Orthoxine-theophylline gave moderate protection against methacholine to one of two patients, and against histamine to 2 of 3 patients. Orthoxine-theophylline by aerosol protected 2 of 6 patients against methacholine, and one of two patients against histamine. The protection given was of short duration in all cases.

D. *Effectiveness in long-term therapy of asthma.* Eight asthmatics in partial remission took Orthoxine-theophylline orally, tablets of 0.2 gm., 4 times daily, as part of their daily regimen for an average of 6 weeks. Four patients reported excellent results, with freedom from attacks and reduction in the amount of other medications required

TABLE 2.—THE EFFECTS OF 250 MG. OF ORTHOXINE-THEOPHYLLINE INTRAVENOUSLY ON 14 PATIENTS WITH ACUTE BRONCHIAL ASTHMA

	Number of Patients		*Reactions*	
Degree of Wheezing	*Before Treatment*	*After Treatment*	*Type*	*Number*
4+	8	0	Faintness	1
3+	5	0	Sweating	0
2+	1	1	Nausea	3
1+	0	5	Vomiting	0
0	0	8	No Reaction	10

TABLE 3.—THE PROTECTING ACTION OF ORTHOXINE-THEOPHYLLINE, ADMINISTERED INTRAVENOUSLY AND BY AEROSOL, AGAINST THE DYSPNEA AND BRONCHOSPASM PRODUCED BY INTRAVENOUS METHACHOLINE AND HISTAMINE

	Orth.-Theoph. 250 mg.	*No. of Patients*	*Maximum Protect. Range (%)*	*Average Vital Capacity (cc.)*		
				Initial	*Maximum*	*After Neos.*
vs. Methacholine i.v.	i.v.	2	0–58	2800	3150	3400
	aerosol	6	0–70	2500	3400	4050
vs. Histamine i.v.	i.v.	3	0–71	2900	3500	4650
	aerosol	2	0–67	2900	3850	4350

during this period. The results were fair in 3 patients, with occasional wheezing relieved by other medications, and one noted no improvement.

Discussion. In animal studies reported by others, Orthoxine-theophylline appeared to be superior to Orthoxine or aminophylline alone[4].

In human subjects, we found that Orthoxine-theophylline gave a higher early blood level than aminophylline when given intravenously, in equivalent theophylline dosage. When compared rectally, aminophylline produced a higher peak level at 2 hours. Adequate blood levels were obtained with both drugs and the significance of the difference in their absorption and release rates cannot be commented upon without further studies. The maximum blood levels with rectal aminophylline occurred at 2 hours; this is the same time interval required for maximum protection against intravenous histamine by rectal aminophylline solution noted during previous studies in our laboratory and corresponds with our clinical impressions about its time of maximum effectiveness[10].

Based on previous protection studies from this laboratory with aminophylline and Orthoxine alone, the protection study results with Orthoxine-theophylline were anticipated. Protection against intravenous histamine was again obtained more often and at higher levels than against intravenous methacholine.

The improvement of vital capacity and maximal breathing capacity after a dose of Orthoxine-theophylline was of significant magnitude, even though the administration of a powerful bronchodilator aerosol increased these measurements further in almost all instances. The intravenous route was the most effective, since additional increases in vital capacity and maximal breathing capacity with the bronchodilator aerosols were less after this route than after the administration of Orthoxine-theophylline by aerosol or by mouth. Orthoxine-theophylline improved the vital capacity and maximal breathing capacity of patients in remission; similar findings have been obtained in the past with such patients when given intravenous aminophylline or a bronchodilator aerosol[6]. However, if one compares the improvement of vital capacity and maximal breathing capacity of the patients in this study with that of other patients in our previous studies, it suggests that intravenous Orthoxine-theophylline is more effective than intravenous aminophylline.

The results obtained with intravenous Orthoxine-theophylline in the treatment of acute bronchial asthma were uniformly good. A dose of 250 mg. to 300 mg. was adequate in most instances and was followed by less side effects than a larger dose. The administration of Orthoxine-theophylline by continuous intravenous drip proved to be of value in terminating status asthmaticus.

From our preliminary observations, it appears that the oral route may be effective for maintenance therapy of the patient with mild, chronic bronchial asthma. However, a larger series of patients is necessary for a more definite evaluation.

The side reactions described in Tables 1 and 2 were observed more frequently with single intravenous injections of Orthoxine-theophylline than with a comparable dose of aminophylline (containing an equivalent amount of theophylline). The nature of the side reactions was similar to those produced by aminophylline.

Five of the 10 patients in our present study who improved with continuous intravenous Orthoxine-theophylline had failed to improve with intravenous aminophylline previously. Fur-

ther trial with continuous infusions of Orthoxine-theophylline in the treatment of status asthmaticus should be undertaken.

Summary. 1. Orthoxine-theophylline, a pure, crystalline compound formed by the unimolecular equivalents of theophylline (the active ingredient of aminophylline) and Orthoxine, a sympathomimetic type agent, was tested for its bronchodilator potency in asthmatic subjects.

2. Theophylline blood levels were determined after intravenous and rectal administration of Orthoxine-theophylline and aminophylline in equivalent dosage.

3. Orthoxine-theophylline by vein or by aerosol showed moderate protection against the bronchoconstrictor effects of intravenous histamine and, to a lesser degree, methacholine.

4. The vital capacity and maximal breathing capacity as well as wheezing and dyspnea of the asthmatic patient were significantly improved by intravenous Orthoxine-theophylline, but to a lesser extent by aerosol and only moderately by oral administration.

5. Orthoxine-theophylline by continuous intravenous drip was effective in terminating status asthmaticus, including 5 cases that had failed to improve on aminophylline intravenously.

6. Orthoxine-theophylline administered by various routes to asthmatic subjects during remission effected an increase of the vital capacity and maximal breathing capacity.

7. The effectiveness of Orthoxine-theophylline in treating bronchial asthma appears comparable and in some instances suggests a superiority to that of aminophylline.

The authors wish gratefully to acknowledge the technical assistance given by Mrs. D. Belgard and Miss D. Grossman in this study.

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ESTROGEN INUNCTION AND SPIDER TELANGIECTASIA IN LIVER DISEASE

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Although it is generally stated[5,7] that estrogen is related to the appearance of spider telangiectasia in patients with liver disease, direct proof of this hypothesis is lacking. Attempts to produce arterial "spiders" by administration of estrogen have not been entirely successful; Bean[2] reported the development of spider telangiectasia in 2 of 3 chronic alcohol addicts following oral and intramuscular estrogen administration, while telangiectasia did not appear after inunction with estrogen[3]. This discrepancy between a widely accepted hypothesis and its experimental substantiation prompted further studies to determine whether percutaneous inunction of potent estrogenic material affects the appearance of arterial "spiders" in patients with liver disease.

Eight patients with portal cirrhosis and one patient with subacute infectious hepatitis were studied. Eight of these patients were males. In four instances the diagnosis was confirmed at necropsy. Pertinent clinical and laboratory findings are shown in Fig. 1. All the patients had spider angiomata and two had developed new ones within 12 days prior to the experimental period.

Ethinyl estradiol,* an estrogen of established potency, was employed in these studies. Five hundredths of a milligram dissolved in 1 cc. of 70% alcohol was anointed over an area on the chest, shoulder or arm measuring 7.6 by 7.6 cm. In each instance, areas were selected that already exhibited unequivocal arterial "spiders." The contralateral area on the chest, shoulder or arm served as a control. In addition the remainder of the skin was under daily scrutiny. In 2 subjects, 0.5 mg. of ethinyl estradiol dissolved in 1 cc. of 70% alcohol was employed. Inunctions were made daily by a physician for 5 days; in one instance this period was extended to 12 days. The treated and untreated control areas were observed clinically and by the use of color photography. Except for one patient who died in hepatic coma 18 days after entry, the follow-up period ranged from 3 to 7 weeks.

The results are shown in Table 1. In only one instance (Case 7) was an increase in vascularity noted in the hormone-treated area. This change appeared on the 21st day after inunctions were started and consisted of a 1 to

*The ethinyl estradiol used in this study was provided by Dr. Edward Henderson, Director, Division of Clinical Research of Schering Corporation, Bloomfield, New Jersey.

2 mm. red area not characteristic of a spider telangiectasis. At the same time, this patient developed a definite new spider telangiectasis in an untreated area. In three other instances (Cases 2, 8 and 9) new arterial "spiders" appeared or existing ones increased in size in untreated areas. In 3 instances (Cases 1, 4 and 9) vascular "spiders" appeared to decrease after hormone application; in two of these, the decrease was observed in the area treated with estrogen.

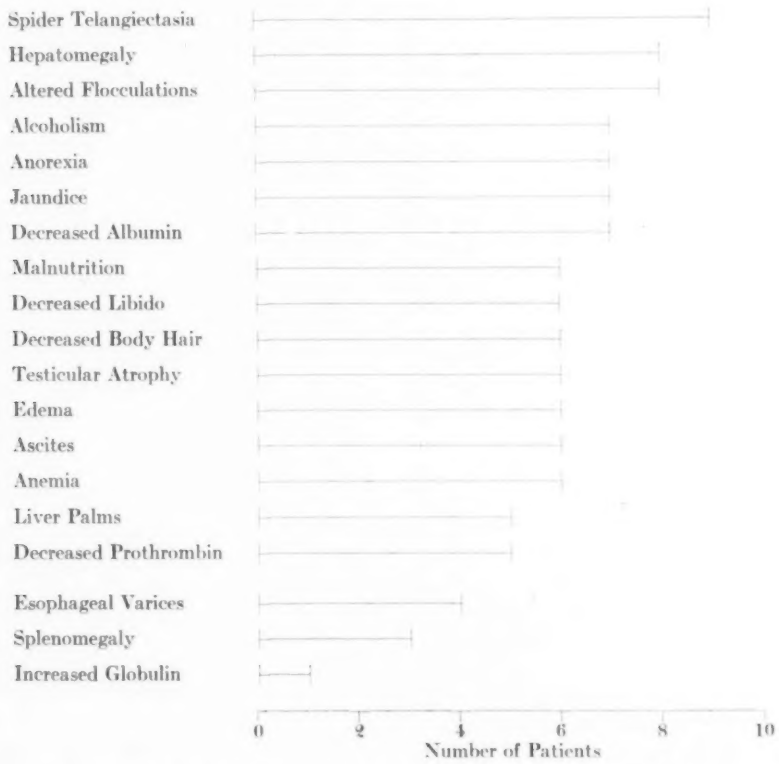

FIG. 1.—Clinical and laboratory data in 9 patients with hepatic disease.

Discussion. Several possible reasons may be suggested for our failure to affect the appearance and number of spider angiomata by estrogenic inunctions in patients with liver disease manifesting active and spontaneous formation of arterial "spiders." These reasons, which include inadequate estrogenic stimulation by virtue of the route of administration, inadequate dosage and low potency of the material used, may be examined briefly.

The possibility that estrogenic stimulation was inadequate because of the percutaneous route of administration appears unlikely. It has been shown in both animals and man that local effects such as mammary enlargement can be produced by estrogenic inunction[6,9,10], and Zondek[11] has demonstrated that inunction is nearly as effective

as the injection of the same amount of estrogen in producing true menstruation after oöphorectomy. The duration of the stimulus (5 days) employed in our studies was short, but Bean's 2 patients with liver disease[2] developed increased size and reddening of their vascular lesions within 6 to 10 days after institution of intramuscular and oral estrogen administration. Furthermore, our subjects and Bean's patient who developed vascular changes in 6 days received comparable total doses of hormone, if calculated on the basis of Emmens[6], however, has demonstrated in animals that systemic effects of absorbed estrogens do not persist beyond 8 to 16 days after inunction. The vascular changes in 3 out of 4 of our cases with postinunction formation of spider telangiectasia appeared 16 days or more after inunction had been discontinued.

Bean[4] has pointed out that the formation of the arterial "spider" probably depends on several factors, including local vascular structure as well as humoral substances. Although this

TABLE 1.—CHANGES IN SPIDER TELANGIECTASIA AFTER ESTROGEN INUNCTION

Patient	*Inunction Area*	*Contralateral Control Area Untreated*	*Other Untreated Areas*	*Number of Days After End of Treatment Change Was First Observed*
1	Decreased	No Change	Decreased	11
2	No Change	No Change	Increased	3
3	No Change	No Change	No Change	*
4	No Change	No Change	Decreased	4
5	No Change	No Change	No Change	
6	No Change	No Change	No Change	
7	No Change	No Change	Increased	16
8	No Change	No Change	Increased	24
9	Decreased	Decreased	Decreased	14
	No Change	No Change	Increased	43

* Died in hepatic coma in 6th week of illness, 6 days after study began.

Allen's studies[1]. That inadequate estrogenic stimulation resulted from low potency of the material used is unlikely since ethinyl estradiol is one of the most potent estrogens known, being 2 to 80 times more effective by weight than other estrogen preparations, depending on the route of administration[1,8].

The spider telangiectasia that appeared in untreated areas in Cases 2, 7, 8 and 9 may have been spontaneous or may have been related to the systemic effects of absorbed estrogen. explanation appeals to us, we have been unable to demonstrate that estrogen, locally applied, serves as the necessary humoral factor.

Summary and Conclusions. Ethinyl estradiol was administered by percutaneous inunction to 9 patients with obvious liver disease and spider telangiectasia. There was no evidence of enhanced formation of arterial "spiders" in the estrogen-treated areas. During an observation period of 3 to 7 weeks, spider angiomata increased in untreat-

ed areas in 4 patients and decreased in 3. In 2 patients a decrease of vascular "spiders" was observed in the hormone-treated area.

We have been unable to show that local inunction of a potent estrogenic substance under the conditions of this study affects the course of spider telangiectasia in patients with liver disease.

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EFFECT OF THE VALSALVA MANEUVER ON PORTAL HYPERTENSION IN CIRRHOSIS

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Observation of changes in the portal venous pressure during transesophagoscopic needling of esophageal varices[1] appears to be the only means by which one may study the effect of the Valsalva maneuver on portal hypertension. This is an important problem to be worked out in elucidating the natural history of portal hypertension and varices, because some authorities believe that varices rupture due to internal hydrostatic pressure, rather than as a result of passive transmucosal erosion. During routine transesophagoscopic determination of portal pressure, demonstration of a quick pressure rise when the patient is instructed to "bear down" is the method by which the esophagoscopist proves to himself that there is free communication between his needle and the varix lumen. However, ordinarily the patient must be told to relax as soon as a substantial rise in pressure is noted, else either the needle will become dislodged by the effort or enough blood will enter the manometric apparatus to result in clotting.

On many occasions during several hundred pressure measurements the opportunity was taken at the conclusion of the procedure to attempt study of the Valsalva effect. In only 15 instances has it been possible to obtain a series of readings throughout and following a maximum Valsalva effort, before the system became blocked by clot. These were biopsy-proved cases of portal cirrhosis, none of which had had any operation or local manipulation to relieve portal hypertension or to obliterate the varices.

Procedure. Esophagoscopy was carried out with the patient horizontal, in the left lateral position. The level of reference for the manometric zero-point was the axis of the esophagus, which is also the level of the right atrium when the patient is in this position. Water was used as the balancing medium in the simple open manometric system. After endoscopic measurement of the extent and diameter of the varices, the resting pressure was measured within the most proximal varix of suitable diameter. The patient was then directed to take a deep breath and to "bear down" as at stool. The rise in the level of the water column was noted until the effort was brought to a conclusion by the patient's inability to hold his breath longer. The patency of the system was then checked again by observing return of the pressure to or close to the initial resting level. The process was repeated as often as possible before clotting supervened.

Results. The column regularly rose quickly and at an even rate through about the first two-thirds of the Valsalva effort, and then moved more slowly to the time at which the patient required another breath. In other words, the pressure was still rising slowly at the conclusion of the prolonged effort. After the pressure had returned to a resting point, it ordinarily remained about 10 mm. above the initial resting level. The resting and maximum pressures recorded for the 15 patients are tabulated (Table 1).

Comment. The Valsalva maneuver affected the portal pressure to a very substantial degree. It is important to

note, however, that the rises were the result of effort which was sustained. Even though the rise was regularly swift at the start of the effort, a strain as brief as a cough caused a variation of only about 40 mm. This is commonly observed during pressure studies. When the esophagoscope is in place, it is very difficult for the patient to carry out a sustained Müller maneuver, and it has not been possible to study this reverse counterpart of the Valsalva maneuver.

TABLE 1.—EFFECT OF VALSALVA MANEUVER ON PORTAL PRESSURE (MM. WATER)

Patient	*Resting Pressure*	*Maximum Pressure Upon Valsalva (repeated in some cases)*
1	460	660
2	245	510, 485
3	420	525
4	420	600, 610, 585
5	390	505
6	280	410
7	510	660
8	485	550, 575
9	425	590, 590
10	310	515, 480
11	495	600, 610
12	305	490
13	510	665
14	390	640
15	455	625, 660

It is not believed that these findings help clarify the mechanisms responsible for initiation of hemorrhage from varices. Once bleeding has begun, however, it is clear that straining may be a potent factor in encouraging blood loss and, more important, in starting bleeding anew after temporary cessation.

Conclusion. The portal venous pressure of patients with portal cirrhosis may rise as much as 265 mm. of water during a sustained Valsalva maneuver, and rather regularly rises more than 150 mm.

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THE INCIDENCE OF THE THROMBOEMBOLIC PHENOMENA ASSOCIATED WITH THE TREATMENT OF ACUTE CORONARY ARTERY OCCLUSION*

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Many investigators have reported a wide variation in the percentage of clinically diagnosed thromboembolic phenomena associated with acute coronary artery occlusion which ranged from 5.9[3] to 33%[10] and Blumer[2], in a review of 945 cases collected from the literature, found an average of 13.9% in 324 cases that had been used as controls in the study of the anticoagulants. However, there are many who have never experienced these high percentages[1,4,8]. A wide difference is also reported in the incidence of mural thrombi from a high of 83% by Levine and Brown[6] to a spread of from 17 to 66% found in a review by Nay and Barnes[7]. LeRoy and Nalefski[5] not only called attention to this but also to the difficulty of statistical analysis. In an attempt to determine the cause of these wide variations in experience, the various methods of treating acute coronary artery occlusion were investigated.

Methods. A series of 983 cases of acute coronary artery occlusion were collected from a teaching and a private hospital. These patients had been attended by many different physicians over a period of from 10 to 25 years, which resulted in numerous combinations and types of drug therapy. There were 28 cases that received treatment but the records were inadequate. The incidence of the occurrence of the thromboembolic phenomena, mural thrombi and mortality, was determined both clinically and by necropsy for each available group. These data were recently presented to the International and American Colleges of Chest Physicians and therefore will only be summarized here. The dose of erythrityl tetranitrate ranged from 15 to 30 mg. every 6 to 8 hours, of papaverine hydrochloride 0.1 gm. every 3, 4, or 6 hours, and of aminophylline† 0.1 to 0.2 gm. every 3 to 8 hours. Occasionally the papaverine hydrochloride and aminophylline were given parenterally.

For each of the tables found herein, a chi-square test has been used to establish whether or not a relationship exists between the methods of classification. Contingency tables were set up from which expected values and chi-square values were determined.

The hypothesis to be tested is whether the two criteria of classification are independent. For example, is the classification *living or dead* independent of *treatment received?* The quantity, chi-square is used to test this hypothesis. Large values of chi-square are inconsistent with the hypothesis: small values are consistent with the hypothesis.

Chi-square values significant at the 5% level indicate there are less than 5 chances

*Aided by a grant from the Central Ohio Heart Association.

†Theophylline in ethylenediamine.

in 100 of the hypothesis being correct; at the 1% level, there is less than 1 chance in 100. The chi-square values significant at the 5% level are marked*, at the 1% level**. Thus in a table where chi-square is large, we can be 95% or 99% confident that the criteria of classification depend on each other. In a table where chi-square is small we can merely say that there is no evidence to support a dependence of classification.

TABLE 1.—INCIDENCE OF EMBOLI DETERMINED CLINICALLY AND PATHOLOGICALLY IN ACUTE CORONARY ARTERY OCCLUSION

Groups	*Number of Cases*	*Number of Emboli*	*Percentage of Emboli*
Hospital care only.			
72.4% mortality	326	26	7.97
Received treatment			
34% mortality	657	43	6.5
Total	983	69	7.0

Chi-square 0.676
3.841 significance at the 5%-level.
6.635 significance at the 1%-level.
The chi-square value falls below the 5%-level, therefore there is no significant difference.

Results. There were 69 persons or 7% of the entire group (983 cases) who had thromboembolic complications, determined either clinically or pathologically, and, in the untreated group of 326 cases, there were 26 or 7.97%. It is probable that some of these persons died before the thromboembolic phenomena could develop, but this factor does not entirely explain the wide variation from the incidence of 36% in the control group and the 14% in the anticoagulant-treated group reported by Wright *et al.*[10]. There were 657 persons who lived long enough to receive treatment and therefore presumably long enough to develop thromboembolic complications, but here again the incidence was only 6.5%.

A comparison of the treatment groups showed a low incidence of emboli (8 or 2%) found both clinically and pathologically in the 386 persons who had received erythrityl tetranitrate, while those receiving papaverine hydrochloride or aminophylline had 6 (33.33%) and 12 (17.64%) respectively (Table 3). A similar comparison of these groups, with the addition of those persons who had also received an anticoagulant, again revealed a wide variation with the lowest incidence of

TABLE 2.—COMPARISON OF THE INCIDENCE OF THROMBOEMBOLIC PHENOMENA IN ACUTE CORONARY ARTERY OCCLUSION AS OBSERVED IN 76 NECROPSIES

Groups	*Percentage of Thromboembolic Complications*
No treatment	7.97
Entire group	7.
Diagnosed at necropsy (No treatment)	28.9
Wright *et al.*[10]	
Control	36
Anticoagulant	14

TABLE 3.—INCIDENCE OF EMBOLISM IN 983 CASES OF CORONARY OCCLUSION: RELATION TO TREATMENT

Type of Treatment	*Number of Cases*	*Number with Emboli*	*Percentage with Emboli*
No treatment	326	26	7.97
Erythrityl tetranitrate	386	8	2.07
Papaverine hydrochloride	18	6	33.33
Aminophylline	68	12	17.64

Chi-square 48.329**
7.815 significance at the 5%-level.
11.341 significance at the 1%-level.
Under all regimens except erythrityl tetranitrate, more emboli occurred than were expected. Chi-square is far greater than the 1%-level, indicating the differences between samples are significant. Thus it may be said that a significantly fewer number of emboli occurred in those patients receiving erythrityl tetranitrate.

emboli (2.5%) in the erythrityl tetranitrate group, while among the others the incidence was 19%. The pathological studies in this investigation showed the same trend and even those persons who had received no treatment had a lower incidence of thromboembolic complications than that reported as a control group for anticoagulant therapy[10]. The entire collected series of 983 cases of acute coronary artery occlusion showed a thromboembolic incidence of 7%, and in 76 necropsies of the persons who received no treatment it was 28.9%. Unfortunately this series does not contain any persons who had been treated with theobromine calcium salicylate, but Gilbert *et al.*[3] reported only 5.9% thromboembolic complications in 118 cases so treated.

Although the persons who received papaverine hydrochloride showed the highest percentage of thromboembolism, those of this group who also received an anticoagulant had the lowest incidence; 8.33% (Table 5).

The total number of patients who received anticoagulants was 77, of whom 13 (16.8%) had embolism. Of those who received only an anticoagulant 14.8% had embolism.

Consideration, however, should be given to the fact that frequently it was impossible to determine whether or not the anticoagulant was given before or after the evidence of thromboembolism, nevertheless the incidence compares favorably with the reported experience of others. There is conclusive evidence that the anticoagulants decrease the mortality and the incidence of thromboembolic phenomena in acute coronary artery occlusion. However, therapeutic agents such as erythrityl tetranitrate and probably some of the xanthine derivatives by their vasodilatation of the coronary circulation show equally good and sometimes better results. It appears that the entire subject of the treatment of acute coronary artery occlusion requires reconsideration and investigation, especially in

TABLE 4.—COMPARISON OF THE INCIDENCE OF EMBOLI IN CORONARY OCCLUSION IN THE VARIOUS TREATMENT GROUPS, WITH OR WITHOUT ADDITIONAL ANTICOAGULANTS.

Treatment	*Number of Cases*	*Number of Emboli*	*Percentage of Emboli*
Erythrityl tetranitrate, with or without anticoagulants	396	10	2.5
Aminophylline, with or without anticoagulants	81	16	19.7
Papaverine hydrochloride, with or without anticoagulants	42	8	19.0
No treatment	326	26	7.97

Chi-square 41.237**

7.815 significance at the 5%-level.

11.341 significance at the 1%-level.

The erythrityl tetranitrate group is the only one in which fewer emboli were observed than were expected. All other groups showed more. Chi-square is much larger than the 1%-level, indicating that the difference between samples is significant. Thus the conclusion is that significantly fewer emboli occurred in patients receiving erythrityl tetranitrate, with or without anticoagulants.

the case of commonly accepted treatments which have high mortalities and a high incidence of thromboembolic complications.

Nay and Barnes[7] have pointed out that any consideration of the thromboembolic phenomena subsequent to myocardial infarction must take cognizance of mural thrombi. In their review of the literature, they reported that the possibility of finding a mural thrombus varies from 17 to 60%. Levine

TABLE 5.—COMPARISON OF THE INCIDENCE OF EMBOLI IN THE CORONARY OCCLUSION PATIENTS WHO RECEIVED ANTICOAGULANTS

	Clinical and Pathological			*Pathological*		
Treatment Group	*Number of Cases*	*Number of Emboli*	*Percentage of Emboli*	*Number of Necropsies*	*Number of Emboli*	*Percentage of Emboli*
Anticoagulants plus						
Aminophylline	13	4	30.76	4	2	50
Papaverine hydrochloride	24	2	8.33	6	0	0
Erythrityl tetranitrate	10	2	20.	2	1	50
Mannitol hexanitrate	3	1	33.3	0	0	0
Anticoagulants alone	27	4	14.8	7	2	28.5
Total	77	13	16.8	19	5	26.

Chi-square 3.318

7.815 significance at the 5%-level.

11.341 significance at the 1%-level.

Use of the chi-square test on these data cannot be considered valid, as in all groups the number of emboli expected falls below five. Five is regarded as the lower limit beyond which expected values must not fall if accuracy is to be preserved.

TABLE 6.—COMPARISON OF THE INCIDENCE OF MURAL THROMBI IN CORONARY OCCLUSION IN RELATION TO TREATMENT

Treatment Groups	*Number of Necropsies*	*Number of Mural Thrombi*	*Percentage*
No treatment	76	34	44.73
Erythrityl Tetranitrate Group			
Erythrityl tetranitrate	7	6	85.7
Erythrityl tetranitrate with anticoagulants	2	1	50.
Erythrityl tetranitrate with various combinations of mannitol hexanitrate and khellin	6	0	0
Total	15	7	46.6
Aminophylline Group			
Aminophylline	16	8	50.
Aminophylline with anticoagulants	4	1	25.
Total	20	9	45.
Papaverine Group			
Papaverine hydrochloride	9	8	88.9
Papaverine hydrochloride with anticoagulants	6	1	16.1
Total	15	9	60.
Anticoagulants alone	7	2	28.57

Chi-square 1.239

7.815 significance at the 5%-level.

11.341 significance at the 1%-level.

and Brown[6] found the highest incidence 83%, or 38 in a group of 46 cases. In our series of 133 necropsies there were 61 or 45.9% mural thrombi (Table 6).

Of the 140 cases with necropsy, there were 7 that did not have an adequate protocol. The remaining 133 were divided into the various treatment groups and the incidence of mural thrombi determined. It was high, from 45 to 60% in the totals of all groups, except in those who had received only an anticoagulant (28.57%). However, analysis revealed that in every group the addition of an anticoagulant to the vasodilator drug lowered the incidence of mural thrombi.

It is evident that all pulmonary emboli complicating acute coronary artery occlusion do not necessarily originate from mural thrombi in the right ventricle, but can be the result of venous thrombosis or thrombophlebitis. Probably the chief causes of these conditions are: lack of movement of the extremities, the enforced bed rest, and the lowered systemic blood pressure, with varying degrees of venous stasis. Also, all of the arterial occlusions occurring in the systemic circulation are not necessarily due to emboli originating from mural thrombi in the left heart, but can be due to arterial thrombosis. Mural thrombi are most common in the ventricles, but 2 were found in that had a mural thrombi only on the right side of the heart. There were 4 persons who had emboli but no mural thrombi.

TABLE 7.—SITE OF EMBOLISM IN RELATION TO THE LOCATION OF THE MURAL THROMBUS IN PATIENTS WITH CORONARY OCCLUSION

Location of Mural Thrombus	*Number of Cases*	*Location of Embolus*		
		Pulmonary	*Systemic*	*Both*
Left side of the heart	17	9	8	
Right side of the heart	3	2	1	
Both sides of the heart	10	8	4	2*

(*In 2 cases there were both systemic and pulmonary emboli)

The locations of the mural thrombus and of the embolus were obtained from the necropsy protocols of 57 persons who had died from acute coronary occlusion (Table 7). Thirty of these persons (53%) had emboli. There were 17 mural thrombi found in the left ventricle, with 9 pulmonary and 8 systemic emboli; 3 in the right ventricle, with 2 pulmonary and 1 systemic embolus; and 10 in both ventricles, with 8 pulmonary and 4 systemic emboli. This high incidence of pulmonary embolism, 21 (70%) of 30 persons having had mural thrombi, has been frequently recognized, and occurs even though most mural thrombi are in the left side of the heart. It is also of interest that a systemic embolus was found once in 3 cases

TABLE 8.—LOCATION OF 53 EMBOLI FOUND AT NECROPSY IN 40 CASES OF ACUTE CORONARY OCCLUSION

Location	*Number*	*Percentage of total number of Emboli*	*Percentage of Necropsies*
Lungs	24	45.28	15.5
Kidneys	15	28.3	11.0
Spleen	6	11.32	4.
Brain	4	7.52	3.
Arm	1	1.88	0.7
Leg	1	1.88	0.7
Small Intestine	1	1.88	0.7
Large Intestine	1	1.88	0.7

the left and 3 in the right auricle. There were 12 cases with thrombi in both auricles and ventricles.

All patients with mural thrombi do not have thromboembolic complications, and when these do occur, there may be more than one lesion (Table 8). There were 40 necropsies that revealed thromboembolism in which the large majority, 24 or 45.28%, were pulmonary. In the systemic circulation, thromboembolism may occur anywhere, but in our series, 28.3% were in the kidneys, 11.32% in the spleen and 7.5% in the brain. The number of necropsies in this series was not large; nevertheless, there was a markedly lower incidence of mural thrombi in those patients who had an anticoagulant. This would appear to show that such therapy has a preventive effect. Of course, all patients who have mural thrombi do not necessarily develop emboli (Table 9). This is emphasized when one examines the several treatment groups. Although the highest percentage of mural thrombi was found in those patients treated with erythrityl tetranitrate, they showed a very low incidence of associated emboli: 16.6%.

There were 449 deaths, a mortality of 45.5% in the entire group of 983 patients with acute coronary artery occlusion. Of these, 326 had received no treatment, with 236 deaths (72.4%). Russek *et al.*[9] reported an incidence of only 0.8% of thromboembolic phenomena in a series of 490 patients selected as "good risks", with a mortality of 3.1%. The 221 deaths, a mortality of 34%, in our series of 658 patients who had received treatment could hardly be considered as representing a group of "good risks". Therefore another series of 142 consecutive hospital admissions for coronary occlusion was collected, including those patients experiencing their first coronary artery occlusion, and with none of the complications listed by Russek *et al.* as contributing to a "poor risk". The mortality rate was 34.5%, with 11 emboli (7.7%). When the persons who died within 48 hours were excluded, there was a remainder of 127 with a mortality of 26.7% and emboli in 0.079%. These mortality rates and incidences of thromboembolism are practically the same as those seen in the entire groups, except when the persons who died within 48 hours were eliminated: then the incidence of thromboembolic complications was very low and confirmed the previously reported effects of "good risk" cases.

A further comparison of the mortality rates in the various groups receiving different types of treatment (Table 10) showed for erythrityl tetranitrate

TABLE 9.—RELATIONSHIP OF EMBOLI TO MURAL THROMBI IN THE SEVERAL TREATMENT GROUPS

Treatment Groups	*Number of Mural Thrombi*	*Number of Emboli with Mural Thrombi*	*Percentage of Emboli with Mural Thrombi*
No treatment	34	16	47
Erythrityl tetranitrate	6	1	16.6
Aminophylline	8	6	75.
Papaverine hydrochloride	8	4	50

Chi-square 0.048

3.841 significance at the 5%-level.

6.635 significance at the 1%-level.

A chi-square test was not applied to this table, because of the small number of cases.

alone, 27.46%; and for erythrityl tetranitrate with and without other drugs, 20.7%; for aminophylline alone, 50%, and for aminophylline with and without anticoagulants, 48%; for papaverine hydrochloride alone, 66.67%; and for papaverine with and without anticoagulants, 50%; and for anticoagulants alone, 37%. The group receiving erythrityl tetranitrate not only had the low-

TABLE 10.—COMPARATIVE MORTALITY IN CORONARY OCCLUSION AS RELATED TO TREATMENT

Treatment Groups	*Number of Cases*	*Number of Deaths*	*Percentage*
No Treatment	326	236	72.39
Erythrityl Tetranitrate Group			
Erythrityl tetranitrate	386	106	27.46
Erythrityl tetranitrate with anticoagulants	10	4	40.
Erythrityl tetranitrate with various combinations of mannitol hexanitrate, papaverine hydrochloride and khellin	80	21	20
Total	477	131	20.7
Aminophylline Group			
Aminophylline	68	34	50
Aminophylline with anticoagulants	13	5	38.5
Total	81	39	48.
Papaverine Group			
Papaverine hydrochloride	18	12	66.7
Papaverine hydrochloride with anticoagulants	24	9	37.5
Total	42	21	50
Anticoagulants alone	27	10	37.05
Vasodilator not stated	28	9	32

Chi-square 160.326**

7.815 significance at the 5%-level.

11.341 significance at the 1%-level.

The observed survival rate is close to, or below the expected value in all groups except erythrityl tetranitrate, in which many more survived than expected.

Chi-square greatly exceeds the 1%-level, indicating that a significantly greater number of patients survived in the erythrityl tetranitrate group than in the others.

est incidence of thromboembolism but also the lowest mortality. In those treated with aminophylline or papaverine alone, the death rates were high, and, when an anticoagulant was also given, definitely lower. This lower mortality and lower incidence of thromboembolic phenomena in those treated with erythrityl tetranitrate (who, however, also had the highest percentage of mural thrombi), would appear to indicate clinically that erythrityl tetranitrate did not have an anticoagulant effect. Our experimental work on animals and investigation with humans has substantiated this opinion. Also the high percentage of mural thrombi can be considered as evidence that the probable effects of erythrityl tetranitrate in reducing the incidence of thromboembolic complications was not due to the dilating effect upon the coronary artery system. It is possible, however, that this effect did increase the cardiac efficiency and thereby decreased the possibility of thromboembolic phenomena originating in the peripheral circulation. This may possibly be the explanation for the low incidence of thromboembolism follow-

ing the administration of the xanthines. Also, the results obtained with heparin and Dicumarol* may probably be due more to the coronary vasodilator of these drugs than to their anticoagulant effect[3].

There is abundant evidence that thrombophlebitis and venous thrombosis are more frequent than is usually recognized clinically, and it is an accepted practice to encourage movement of the extremities, in order to prevent the thromboembolic complications. However, an unexplained inconsistency apparently exists, in that those persons treated with erythrityl tetranitrate had the so-called conservative treatment with 6 weeks of absolute bed rest. However, there was no restriction or caution in regard to movement of the arms and legs after the first 5 to 7 days. There is also the possibility that the vasodilator drugs may have an effect upon the peripheral circulation.

In a personal communication, Dr. E. Sterling Nichol raised the valid criticism that some physicians, hospital staffs and pathologists were more thorough than others in their search for, and diagnosis of, thromboembolic phenomena. Therefore from the entire group there were selected 730 patients who had come under the direct clinical and pathological observation of the authors (Table 11). This group revealed clinically 4.8% and, in 76 necropsies, 24% of thromboembolism. A group of 253 patients who were under the care of various physicians had a clinical incidence of embolism in 13%, and, those coming to necropsy, a pathological incidence of 30%. The probable explanation of the lower clinically-diagnosed incidence is that this group contained practically all of those treated with erythrityl tetranitrate. It was also realized that some of the patients in this group were seen and diagnosed 15 to 20 years ago. Therefore another group of 150 patients with acute coronary artery occlusion seen in this hospital during the past 5 years was studied and they showed approximately the same low incidence, 6.2%.

TABLE 11.—COMPARISON OF THE INCIDENCE OF EMBOLI IN TWO HOSPITAL GROUPS: ONE OF THEM UNDER THE DIRECT OBSERVATION OF THE AUTHORS

	Clinical and Pathological			*Pathological*		
Hospital Groups Observed by	*Number of Cases*	*Number of Emboli*	*Percentage of Emboli*	*Number of Necropsies*	*Number of Emboli*	*Percentage of Emboli*
The Authors	730	35	4.8	78	19	24
Others	253	34	13.	62	19	30

Chi-square 21.372** Chi-square 0.709

3.841 significance at the 5%-level.

6.635 significance at the 1%-level.

Conclusions. There is a lower incidence of mural thrombi in persons with acute coronary artery occlusion who have received anticoagulants.

The lowest death rate and lowest incidence of thromboembolic complication were in the group of patients who had received erythrityl tetranitrate.

The routine or mandatory use of an anticoagulant in every case of acute coronary artery occlusion is not advocated.

*Bishydroxycoumarin.

Further investigation is required to determine the clinical indications for the use of the anticoagulants.

A re-evaluation of the treatment of acute coronary artery occlusion is indicated, especially in regard to the role of the efficient vasodilator drugs, such as erythrityl tetranitrate, in lowering the mortality and preventing thromboembolic complications. This is necessary in order to establish a more accurate knowledge of the true incidence and cause of these thromboembolic phenomena.

The technical assistance of Stewart M. Rose is acknowledged.

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THE IMPORTANCE OF TRYPSIN IN INFANCY AND CHILDHOOD
PART II. CLINICAL CONSIDERATIONS.

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IN a previous paper[25] the biochemical and physiologic properties of trypsin have been discussed. In the present review, studies of published reports on the clinical aspects of trypsin have been examined in the light of their possible application to pediatrics.

Very few investigations have been concerned with the time of appearance of intestinal tryptic activity during fetal life. The monograph of Werner[82] is based on the postmortem histochemical demonstration of the presence of trypsin in the pancreas of 42 prematures; there is an appreciable increase in the proteolytic enzyme content of the pancreas from the time of its appearance around the fourth month of fetal life until the time of birth. More recent and elaborate studies are in agreement with these findings. Gschwind[24] studied the tryptic activity of 38 prematures and 18 newborns and found the proteolytic activity to be proportional to increasing maturity with wide ranges in each weight group. Similar results were recorded from measurements made by Johnstone[30] and Farber and his coworkers, quoted by Smith[66]. It is of interest to note that trypsin and meconium are demonstrable in the bowel of the human fetus at approxi-

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mately 4 or 5 months' gestation. It is generally accepted that meconium contains some trypsin activity[30]. However, inconsistent findings in the hands of some workers[61] indicate the necessity of accumulating more data on this subject before drawing any conclusions.

As to the part played by trypsin during infancy, it is deduced from the work of Vazquez[77] that among the three chief pancreatic enzymes the most constant and the one which first reaches an adequate level is trypsin. By 3 or 4 months, its concentration in the infant's digestive tract reaches the average values obtained during the first 2 years of life.

It is not possible to state with certainty the trypsin output in infants with normal digestion, because of the widely different figures for the mean value reported by various authors: 200 units per cc. by Farber[14] and 99 units per cc. by Davison[33]. Wide ranges of activity have been found with the same titration technique by the same authors[14,19,22,33]. For example, extremes of 19 to 372 units per cc.[14,33] seem to fall within the range of normal physiologic function. Apparently there is no correlation between the interval after meals and the concentration in enzyme units per cc. of duodenal juice. Under fasting conditions, the rate of formation of duodenal fluid ranges from 4 to 31 cc. per hour (mean 8 cc.), or 192 cc. in 24 hours[33]. Characteristically the rate of formation of duodenal fluid has a cyclic distribution over a 24-hour period.

It is apparent from the above considerations that our estimation of the proteolytic function of the digestive tract in premature and newborn infants is essentially qualitative. Whether premature infants would thrive better if fed proteins in the form of hydrolysates is a disputed question. In 1943, Magnusson[44] supplemented the intake of breast-fed premature infants with casein hydrolysates. When compared with infants given a supplement of whole casein identical in caloric value but requiring digestion by their own proteolytic enzymes, the ones receiving casein hydrolysate gained weight more rapidly. Werner[82], judging from his own studies on tryptic activity in prematures, also advised the use of predigested proteins. However, the findings presented by Madey and Dancis[43] cast doubt on the need for substituting split for unsplit proteins in the premature infant's diet. A slightly better performance on calcium caseinate than on hydrolysate was found after their group of premature infants had reached the 30th day of life. To explain such findings the possibility of valuable amino acid complexes being lost during the process of hydrolysis was suggested. Additional evidence to support the theory that the digestive capacity for protein is physiologically adequate in the premature infant has been given by the studies of Gordon and his associates[21]. They have found that good nitrogen absorption occurs with a protein intake as high as 9 gm. per kg. of body weight per day in premature infants.

Diagnostic Implications. METHODS. Trypsin estimation has its main value in determining changes of pancreatic function. The assay for trypsin can be done by a number of approaches: (1) Direct duodenal drainage. (2) The determination of the proteolytic activity of the stools. (3) The indirect methods of absorption of a protein as reflected in the blood. (4) The indirect method of determining N^2 intake and output as a partial reflection of the tryptic activity of the pancreas.

1. The duodenal intubation initially utilized a single-lumen gastroduodenal tube. Since trypsin shows its maximum activity at pH 8, it was later felt that

better results would be obtained by exclusion of the gastric juice. To accomplish this purpose a double lumen tube is placed into the duodenum as far as the ligament of Treitz with the end of one lumen in the stomach. Suction is placed on both lumens. Some authorities who feel that gastric juice has not decreased the pH or diluted the duodenal juice continue to use single-lumen tubes and collect by gravity flow. Secretin 1 unit/kg. has been recommended as a pancreatic stimulant; however, the difficulty in obtaining pure secretin has been unsurmounted as yet[19]. In addition, secretin stimulates the total volume and HCO_3 secretion, producing enzymes by the simple process of "washing out" of the pancreatic exocrine system. Finally, some recent preparations of secretin have been contaminated with other agents producing a marked biliary flow and, in certain instances, causing sensitization to further injections. Urecholine has been used with some success in total doses of 1.2 mg. intramuscularly. In general, however, with patience, duodenal drainage in children provides sufficient fluid without any additional stimulation.

Several methods for trypsin titration have been reviewed in Part I of this paper[25]. Most of these procedures are complex and require more time and effort than a hospital laboratory can devote to them. The direct method of Riggs and Stadie[56] and that of Fermi[15], later modified by Andersen and Early[5], have been selected by most laboratories because of their simplicity and sufficient degree of accuracy for diagnostic purposes. The former procedure has been described in Part I. Andersen's method consists essentially in incubating at 37° C. for one hour, serial dilutions of duodenal juice with a 7.5% solution of gelatin acting as a substrate. The mixtures are then stored in a refrigerator for 24 hours. The reading is taken by inverting the tubes: the lowest dilution of juice by which gelatin has been liquefied is considered as the end point.

2. A practical contribution to the diagnosis of tryptic deficiency was the screening gelatin film test proposed by Shwachman, Patterson and Laguna in 1949[64]. Similar work was reported, in 1930, by Harrison[26], quoting the studies of Este Emery. This screening test, performed on the stool, is based on the observation that when properly prepared photographic film is brought into contact with solutions of active trypsin the gelatin is digested.

This procedure releases the silver and clears the film to a degree proportional to the activity of trypsin[64]. Gaffney[17] recommends the use of Eastman Kodak dental film to obtain valid results when incubating a dilution of stools at 37° C. for one hour. In all instances, a control must be run to determine the sensitivity of the film emulsion.

Negative film tests are frequently encountered in older children whose pancreatic secretions are normal. Constipation or obstipation is the most frequent cause of such negative tests, by permitting destruction of the enzyme by intestinal bacteria. When slow movement of feces is the cause of a negative test, the giving of a laxative will make the stools become positive; with pancreatic fibrosis they will remain negative. When, under proper circumstances, the gelatin film test shows no digestion in all dilutions of the fecal suspensions, no further studies of that specimen are necessary, though several more examinations on subsequent specimens are advisable to confirm the complete and persistent absence of enzyme.

A positive reaction in a 1:100 suspension is strong evidence for good

pancreatic function, since few fecal organisms can produce enough enzyme to digest gelatin in that dilution. When the test is positive in only the 1:5 and 1:10 dilutions, the following steps are suggested: 1) The fecal specimen should be studied bacteriologically for the presence of gelatin-liquefying bacteria. 2) A suspension of twice the minimal concentration of the stool specimen which yields a positive film test should be mixed, separately, with equal amounts of a solution containing 2 mg. per liter of soy bean trypsin inhibitor, using physiologic saline as a control. Complete inhibition of gelatin liquefaction by trypsin inhibitor in the presence of a positive control is indicative of human trypsin rather than bacterial enzymes. Another source of error may be contamination of the stools with urine, since urine often contains a proteolytic enzyme.

3. A further approach for evaluating the proteolytic activity of the pancreas is to determine the rise in the blood after giving a test feeding of protein. Two such methods have been the determination of amino-nitrogen and glycine in the blood.

From the results presented by West, Wilson and Eyles[83], it appeared that gelatin fed to a group of patients suffering from cystic fibrosis of the pancreas failed to produce significant changes in the amino-nitrogen level of the blood, as compared to a rise exceeding 2.0 mg. per 100 cc. in children with normal proteolytic function of the pancreas. This difference seemed of sufficient magnitude and constancy to constitute a practical test for this disorder. Other observations by the same authors have shown that gelatin seems a better test meal than casein as reflected by higher levels of amino-nitrogen in the blood. Casein hydrolysates were of no diagnostic value when fed to patients with cystic fibrosis of the pancreas, since it is well metabolized by these patients in the absence of tryptic activity.

A simplification of the blood amino-nitrogen levels was introduced by Christensen and Shwachman[9]; determination of the plasma concentration of the single amino acid, glycine, was substituted for the technically more complex determination of amino-nitrogen. The test meal consists of 1.5 gm. of gelatin per kg. of body weight dissolved in 30 cc. of warm water, given 6 to 12 hours after the last meal. Venous blood is sampled just before and again 2½ hours after the feeding. The glycine is determined according to Alexander's method[1]. A rise in blood glycine to more than 2.5 times the fasting blood level may be expected in children having normal tryptic activity of the pancreas. Patients with no tryptic activity in the duodenal juice show less prominent rises, if any.

4. A more elaborate method which, in part, may reflect the proteolytic activity of the pancreas is the estimation of the nitrogen intake and output. Shohl, May and Shwachman[62] conducted metabolic studies relating nitrogen content of the stool to various protein diets. They found that the total fecal nitrogen of patients with cystic fibrosis of the pancreas is three or four times that of normal infants. However, in these same patients the amount of nitrogen per unit of weight of feces shows little variation when compared to that of normal infants. Casein hydrolysates fed to these patients resulted in low fecal residue with low nitrogen excretion.

Lavik and his associates[37] have utilized radioisotope I_{131} in a similar type of study. *In vitro* studies showed that 88% or more of the I_{131} remained attached to the tyrosine of the protein molecule. They administered a known amount of I_{131} labeled protein orally and measur-

ed the amount of isotope excreted in the feces. In 5 children with pancreatic fibrosis, the fecal excretion of I_{131} was 10 to 40% that of the amount ingested, compared with a maximal fecal excretion of 6% in a series of 10 children with diseases which did not involve the gastrointestinal tract.

EVALUATION OF TRYPSIN IN PATHOLOGICAL STATES. Utilizing these techniques, workers became interested in evaluating pancreatic dysfunction in several pathologic conditions of infancy and childhood. Most reported studies have included patients with cystic fibrosis of the pancreas as a basis for comparison.

A selective decrease of pancreatic trypsin in children with normal lipolytic and amylolytic activity has been reported by Lowe *et al.*[40], Farber *et al.*[14], Veghelyi[79], Gibbs *et al.*[20], and McDougall[46]. It is not clear at the present time whether this phenomenon represents an intermediate state of cystic fibrosis of the pancreas or a true selective trypsin deficiency. Andersen[3] has indicated that trypsin is a reliable index of the total pancreatic function. The evidence from various authors including Freudenberg[16] seems to indicate that there is close relationship in the secretion of the three pancreatic enzymes in the healthy child.

Veghelyi[79] studied the pancreatic enzymes in the duodenal juice during the incubation period (in 3 patients) and during the first day preceding the enanthem and exanthem (in 29 patients) of scarlet fever. Abnormal values were found in 26 patients. Early in the disease, the output of pancreatic enzymes was high above normal, while the values in the blood were decreased. After the first week, this ratio was reversed and the enzymatic activity in the duodenal juice became transitorily depressed. Of the three pancreatic enzymes, the output of lipase was the one most frequently affected. Low values for trypsin alone were found in one case, for both trypsin and lipase in 6 patients and for all three enzymes in 14 cases. This phenomenon reverted to normal in the majority of the patients and was ascribed to an acute pancreatitis concomitant with scarlet fever. The author suggested that pancreatic deficiency be considered in all cases where retarded development appears subsequent to a recent attack of scarlet fever.

Additional evidence of impairment of pancreatic secretion during acute infections is provided by the early descriptions of the "Pancréatite ourlienne" in the French literature, as far back as 1897[11]. Later, Simonin[65], and Moutier[50] made comprehensive studies of this fairly frequent complication associated with parotitis. In this country, Radin[52] found 14 patients with clinical signs of pancreatic involvement in an epidemic of 6000 cases of mumps. In spite of the voluminous amount of publications on this subject, very few patients have had a thorough enzymatic investigation. The importance of the amylase test as a diagnostic procedure and the recognition of glycosuria and diabetes as sequelae of parotitis have been stressed for many years. It was Veghelyi[78] who first reported the duodenal enzymatic changes in mumps pancreatitis. In 2 children convalescing from mumps parotitis, a diagnosis of acute pancreatitis was established. Both cases presented low normal values for duodenal amylase with traces of lipase and trypsin. One of these 2 children was found to have persistent low lipase values and subsequently died with pancreatic insufficiency.

Veghelyi demonstrated that pancreatic enzymes were diminished early in pancreatitis complicating various infections and were the last laboratory abnormalities to return to normal. He also

believed that a subclinical decrease in the production of enzymes is more frequent than glycosuria and that the exocrine activity of the gland is more susceptible to noxious agents than the endocrine.

Farber, Shwachman and Maddock[14] found no proteolytic pancreatic deficiency in toxic or infectious hepatitis, asthma, eczema, dwarfism, cretinism, pertussis, congenital atresia of the bile ducts, or nephrosis. The same authors described 2 patients with hypoglycemic convulsions who developed appreciable tryptic depression after surgical removal of 80% of the pancreas. In spite of this procedure, adequate pancreatic function was present to avoid clinical signs of pancreatic insufficiency.

Studies of enzymatic function have been extended to patients showing signs of various intestinal or nutritional disorders. Kajdi *et al.*[33] recorded a decrease in the trypsin and amylase content of pancreatic juice from one child with acute diarrhea. Nine convalescent children presenting transitory diarrhea and one case of sprue were included in this series. All these patients achieved the requirements for normal pancreatic activity. McDougall[46] showed that in a series of 165 children experiencing chronic intestinal and nutritional disorders and referred with a tentative diagnosis of celiac syndrome or cystic fibrosis of the pancreas, 25 had suppression of lipase activity in conjunction with a normal level for trypsin and amylase, and 16 were deficient in amylase in conjunction with normal lipase and trypsin. There were no children with suppressed tryptic activity in the presence of normal lipase and amylase. Andersen[3] observed the presence of functional pancreatic deficiency in 3 children with severe marasmus. All three pancreatic enzymes were depressed during the acute phase and were restored to normal upon recovery. According to the author, this illustrates well the inhibition of various organ activities during inanition.

More recently the hypothesis of an excess of tryptic activity has been suggested as being responsible for the colonic involvement in ulcerative colitis. Two groups of workers[35,81], however, have shown the absence of any definite increased activity of trypsin in this pathologic entity.

Trypsin in Substitution Therapy. The activity of trypsin is applied predominantly in the form of a pancreatic extract for the therapy of pancreatic deficiency. The U. S. Pharmacopoeia specifies that pancreatin must be able to change not less than 25 times its weight of casein into proteoses.

It is safe to say that the dosage of pancreatic extracts is still largely empiric. It was learned from the observations of Farber *et al.*[14] that subtotal pancreatectomy deprives the patient of normal enzymatic activity to a certain degree but not proportionally to the mass of pancreas removed. An essential enzyme like trypsin must reach a critically low level prior to the development of clinical symptoms. In replacement therapy using trypsin, results may be obtained only when the activity of the material exceeds the physiologic threshold under which proteolytic digestion takes place. It is now recognized by most investigators that the choice of a proper concentrated pancreatic extract and in large doses is of primary importance. Powdered pancreatin has been used principally for substitution treatment in infants. Enteric coating makes the preparation occasionally more palatable and easier to handle, but does not markedly protect from gastric acidity[2]. Recently a pancreatic preparation Viokase, richer in all pancreatic factors and much more

stable, has become available (Schwachman[63]).

DOSAGE. After complete pancreatectomy it has been found that doses up to 20 gm. of pancreatic extract daily are necessary for optimal nitrogen absorption[85]. Most workers previously have suggested that 1 gm. for 6 to 8 oz. of formula be used for the infant, and 2 to 6 gm. for the older child[2,13,34,53,72] divided into 3 doses. Lowe[39] has suggested larger doses: between 6 to 12 gm. per day. The general tendency seems to be to use higher doses to approximate more closely the physiologic output of pancreatic enzymes[85].

GENERAL APPRAISAL OF SUBSTITUTION THERAPY. Clinically, the therapeutic efficacy of substitution with pancreatic substance in children with pancreatic insufficiency has been difficult to evaluate because of the progressive nature of the pulmonary components of the disease. Consequently, most of the supportive data for substitution therapy are based on clinical impression and indirect absorption and balance measurements.

Andersen[4] has indicated that pancreatin improves the utilization of food considerably in the marasmic patient with cystic fibrosis. Only slight benefit was noted by balance studies in children who had mild deficiency symptoms. Lowe[39] and Gibbs[18] have suggested that pancreatic extracts may have an unfavorable effect on the ravenous appetite of children with cystic fibrosis of the pancreas. However, this abatement of the appetite in this instance may be a reflection of a more physiologic digestive capacity and a better absorption.

Shohl, May and Shwachman[62], and West, Wilson and Eyles[83] have shown by balance studies that pancreatin may improve the protein retention in patients with cystic fibrosis of the pancreas. This has been confirmed by radioisotope tracer studies[37]. A 50% decrease in the fecal excretion of I_{131} bound to protein was found in 2 of 4 children with cystic fibrosis of the pancreas when pancreatin was used in the test meal.

Pancreatic extract has also been used in acute diarrhea[14] and found to reduce the number of stools; however, this has not been further described or come into common use.

Other Uses of Trypsin. Trypsin seems to be necessary for the transformation of profibrinolysin to fibrinolysin in the living organism. This potent fibrinolytic activity of trypsin has broadened its use in many diseases, both in diagnosis and therapy, especially since the recent availability of purified trypsin commercially for parenteral and topical administration.

CHANGES IN FIBRINOLYTIC ACTIVITY IN VARIOUS DISEASE STATES. In acute pancreatitis there is a prolonged prothrombin time and a decrease in fibrinogen[7]. A suggested explanation for this finding is that trypsin becomes elevated within the vascular system as the result of pancreatic stasis. Similar changes in the components of the blood have been reproduced experimentally in animals by the administration of trypsin[70].

In cases of unexplained bleeding which have occurred in trauma, extensive surgery, burns, shock, transfusion reactions and severe liver diseases, trypsin-like activity has been detected in the blood[67]. Conversely, the presence of an increased concentration of trypsin inhibitor acting as antifibrinolysin in the plasma and urine associated with a variety of illnesses has been described by Butler *et al.*[8], Waldvogel *et al.*[80] and Dillard[12]. Increased trypsin inhibitor excretion is demonstrable in bacterial pneumonia, rheumatic fever and meningitis, and after surgery[12].

A rise in serum trypsin inhibitor titer has been also correlated with advanced

malignancy and leukemia[80]. No relationship has been established between the plasma and the urinary trypsin inhibitor. Waldvogel ascribes these findings to endocrinologic influences. According to Ungar and Damgaard[73] the inactivation of fibrinolysin by antifibrinolysin may be regulated by ACTH.

An additional diagnostic use of trypsin was investigated by Mirsky[48]. On subcutaneous injection of a 1% solution of crystalline trypsin, 70% of patients convalescing from rheumatic fever and 13% of a control group developed subcutaneous nodules. The author proposed that the individual who cannot inhibit adequately this local nodular reaction may prove more susceptible to the development or recurrence of rheumatic fever. Schlamowitz and DeGraff[59] demonstrated the development of subcutaneous masses on injection of trypsin but no palpable alterations with inactivated trypsin; this suggests that enzyme activity plays a role in the formation of the nodules. Grob[23], in 1943, showed that the local reaction to subcutaneously injected trypsin is inversely proportional to the antiproteolytic activity of the serum; this correlates well with the low antiproteolytic activity found in rheumatic fever.

Searching for a more reliable method of determining the tryptic activity of the blood, Innerfield *et al.*[27] found that the antithrombin titer of the blood would more closely link to this enzyme than any other circulating antitryptic substance. Accordingly, this test was utilized to control intravenous infusions of trypsin. They concluded that this test could be especially useful in the detection of the early cases of cystic fibrosis of the pancreas and in the establishment of a pathologic classification of its evolution. MacFarlane[41], who tried to reproduce these findings, restricted the potential value of this test to the confirmation of clinical diagnosis.

THERAPEUTIC IMPLICATIONS. Favorable reports are available regarding the value of trypsin in the digestion of fibrinous and purulent exudates. Complete cellular death seems a prerequisite for effective tryptic activity; nonviable cells and tissue, mucin, fibrin and protein-split products are equally affected by trypsin; viable tissue is apparently immune to its activity by virtue of its antitryptic activity.

It has been used topically for debridement in burns, wounds and decubitus ulcers[10,42,47,49,54,58,69,84]. Insufflation with powder trypsin seems to be the best mode of local therapy[49] in easily accessible areas. If wet dressings or irrigations are desired, a solution of 250,000 units in 25 cc. of Sorensen's phosphate buffer solution has been recommended. Very few sensitivity reactions have been reported.

Trypsin has also found a use in empyema[32,54,55,57,71] caused by tubercle bacilli and other organisms, in hemothorax[45] and osteomyelitis[54]. The pleural fluid becomes less viscid and decreases in amount after introduction of trypsin into the thoracic cavity. As much as 250,000 units in 50 cc. of buffer solution has been instilled into the thoracic cavity. Severe chest pain may be an annoying complication, but a topical anesthetic agent may minimize this problem. Antihistaminics have been given during this therapy as a prophylactic measure against an acute systemic reaction. The results in empyema have been difficult to evaluate, but trypsin seems to have been effective when other conservative therapy has failed.

In conditions where thick and inspissated secretions in the bronchial tree are a prominent feature of the disease process, aerosol trypsin is a useful adjunct to other conventional forms of

therapy. Such conditions are atelectasis, cystic fibrosis of the pancreas associated with bronchiectasis, asthma, and bulbar poliomyelitis complicated by atelectasis[6,38,51,60,68,74,76,86].

The dosage schedule[38] is started with 50,000 units in 1 cc. of buffer solution. This can be repeated as often as three times daily. The dosage may be increased to 200,000 units if the previous doses have been well tolerated. The solution is nebulized with an oxygen flow of 5 to 6 liters per minute within a period of 15 minutes. The intranasal route is advocated for small infants. When cooperation is obtainable from older children, the aerosol may be delivered by nebulizer or mask, with due precautions to protect the eyes. Antihistaminics are recommended to prevent any untoward systemic effects. Contraindications[75] to aerosol therapy are status asthmaticus, hemoptysis, and erosions of the pharynx or tracheobronchial tree.

Innerfield[28] has reported on a series of patients treated with intravenous trypsin. The final decision as to the value and danger of this form of therapy is still in doubt[36]. Further knowledge as to the proper selection of patients and optimal dosage will be gained by careful laboratory and clinical trial.

Summary. In this review the physiology and pathological physiology of trypsin in infants and children have been described. It has been shown that pancreatic trypsin is demonstrable as early as the 4th month of fetal life and reaches an adequate level by birth.

Assays for trypsin have been done by (1) duodenal intubation, (2) determination of proteolytic activity in the stools, (3) blood absorption studies of an ingested protein, and (4) balance studies on nitrogen intake and output as a partial reflection of the tryptic activity of the pancreas.

Cystic fibrosis of the pancreas is the primary pediatric problem referable to pancreatic insufficiency and a decrease in trypsin. Transient decreases in trypsin production have been recorded in scarlet fever, mumps, and acute diarrhea. No changes were found in chronic intestinal conditions and malnutrition.

In the form of pancreatin, trypsin has been used for substitution principally in cystic fibrosis of the pancreas. The suggested doses have varied between 2 to 6 gm. divided into 3 daily doses with meals. Recently larger doses between 10 and 20 gm. have come into more widespread use. Pancreatin seems to show its most positive effects in marasmic children with pancreatic fibrosis.

The fibrinolytic activity of trypsin has widened its role in therapy. It has been used with varying degrees of success in empyema, local debridement, bronchiectasis, atelectasis, and the pulmonary manifestations accompanying pancreatic fibrosis. The results have been encouraging enough to make it an agent worthy of careful trial and study.

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TOXEMIA OF PREGNANCY

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THE present review will be selective, for a number of reasons. The hormonal aspects of toxemia of pregnancy have been reviewed recently by Smith and Smith[117], the renal aspects by Chesley[24], and the older work on weight changes, water and salt balance and edema development by Chesley[22]. A new edition of Dieckmann's[34] comprehensive book was published in 1952 and a superbly organized monograph by Page[92] appeared in 1953; this contains much information marshalled in support of his hypothesis that placental ischemia may be the cause of preeclampsia-eclampsia. Treatment, nutritional factors, and several other aspects are intentionally omitted from the present review, either through sloth, prejudice, or lack of comprehension.

The American Committee on Maternal Welfare[41] recently has revised the classification of the toxemias of pregnancy. The revision is more extensive than may appear at first glance and its strict application will greatly increase the incidence of diagnosed toxemia. As now defined, "toxemia of pregnancy" comprises some of the "disorders encountered during gestation, or early in the puerperium, which are characterized by one or more of the following signs: hypertension, edema, albuminuria, and in severe cases, convulsions and coma." One disease not specific to pregnancy is included, namely, hypertensive disease; others such as glomerulonephritis are not. The classification is as follows:

I. Acute toxemia of pregnancy (onset after the 24th week)
   A. Preeclampsia
      1. Mild
      2. Severe
   B. Eclampsia (convulsions or coma, usually both, when associated with hypertension, proteinuria or edema)

II. Chronic hypertensive (vascular) disease with pregnancy
   A. Without superimposed acute toxemia (no exacerbation of hypertension or development of proteinuria)
      1. Hypertension known to have antedated pregnancy

2. Hypertension discovered in pregnancy (before 24th week and with postpartum persistence)

B. With superimposed acute toxemia

III. Unclassified toxemia (data insufficient to differentiate the diagnosis)

Another group, Recurrent Toxemia, has been defined by the Committee but not included in the skeleton outline. This diagnosis is made if the patient with toxemia gives a history of previous toxemia, was normal between pregnancies and is normal at follow-up examination.

The criteria for diagnosing toxemia are:

I. Hypertension. Systolic pressure of 140 mm. Hg or more, or diastolic pressure of 90 or more, or an increase in the systolic pressure of 30 mm. or more, or an increase in the diastolic of 15 or more. These readings must be observed on at least 2 occasions at least 6 hours apart. The specified increases, in hypertensive patients, make the diagnosis of superimposed acute toxemia.

II. Edema. The diagnosis of toxemia on the basis of edema alone can be made only when there is edema of the hands or face, present in the morning and clinically evident.

III. Proteinuria. The diagnosis of toxemia on the basis of proteinuria can be made when clean or catheterized urines, on 2 or more successive days, show an unequivocal cloud of protein precipitated by any recognized test, or the excretion of 0.5 gm. or more of protein per 24 hours, for at least 2 consecutive days.

Preeclampsia is classified as "severe" if any one of the following signs and symptoms are present. If none are present, the preeclampsia is classified as "mild":

I. Blood pressure of 160 or more systolic, or 110 or more diastolic, on at least 2 occasions 6 hours or more apart, with the patient at bed rest.

II. Proteinuria of 5 gm. or more in 24 hours (3 or 4 plus on qualitative examination).

III. Oliguria (400 cc. or less per 24 hours).

IV. Cerebral or visual disturbances.

V. Pulmonary edema or cyanosis.

The superimposition of acute toxemia upon hypertensive disease is diagnosed if the systolic pressure increases by 30 mm. or more, or if the diastolic pressure increases by 15 mm. or more, or if a significant degree of proteinuria appears.

Unfortunately, there is no stipulation as to what baseline is to be used in determining the increase in blood pressure. About one-third of women who begin pregnancy with hypertension show significant drops in the blood pressure throughout most of pregnancy[16,27,98]. As they approach term the blood pressure characteristically rises, often to about the prepregnant level. If the usual level in pregnancy be taken as the baseline, many such patients might be classified as having superimposed preeclampsia, probably erroneously.

Another troublesome aspect posed by the hypertensive woman's behavior in pregnancy is that an appreciable proportion of them have drops of the blood pressure into the normal range during most of the gestational period. Prepregnancy blood pressures seldom are known and when such a hypertensive patient shows the typical rise in blood pressure late in pregnancy, after a series of normal readings, she is likely to be misclassified as having preeclampsia.

Necessarily, the classification is arbitrary. Preeclampsia very occasionally appears before the 24th week and hypertensive disease may first become manifest after the 24th week. Recurrent toxemia may be an entity, or it may be preeclampsia, or it may be a sign of vascular disease. Many believe that hypertensive disease predisposes to preeclampsia, but Dieckmann[34] thinks that the syndrome represents an exacerbation of the hypertensive disease and is not preeclampsia. Finally, there are those who believe that all of these subgroups are merely the spectrum of hypertensive disease as colored by pregnancy.

HOW MANY DISEASES? For the reasons outlined, clinical and laboratory tests have been sought to differentiate the toxemias. In general, each author of such a test has been able to differentiate the toxemias into dissimilar syndromes and other investigators have confirmed the differentiation. In general, such studies have been concerned with a single one of the several tests proposed, although Govan *et al.*[47] have used 3 in conjunction. It has not been ascertained whether a battery of such tests would consistently point to the same syndrome in a given patient. This is an important consideration, for if all tests pointed to the same diagnosis in a given patient, we could be more confident that these subgroups of toxemia really are disease entities. If, on the other hand, a patient were preeclamptic by some tests and hypertensive by others, then we might suspect "toxemia" to be a single disease with varying manifestations from case to case.

In addition to some of the tests which have been applied to the differential diagnosis, certain other relevant observations will be reviewed. One of the difficulties in the interpretation of the results of different investigators is the wide variation in criteria used for classifying the toxemias. The first Table in Dieckmann's[34] book compares the relative frequencies of the subgroups of toxemia in 8 large hospitals: of all toxemias, preeclampsia makes up anywhere from 39% in one hospital to 90% in another. Obviously the criteria for classifying a case as preeclampsia must be far different from hospital to hospital. If test "X" seems to be specific for preeclampsia in a hospital where 80% of the toxemias are called preeclampsia, the specificity obviously will not be confirmed in a hospital where only 40% of the toxemias are classified as preeclampsia.

I. *Pitressin test.* Dieckmann and Michel[35] and, independently, Schockaert and Lambillon[108] found that patients with preeclampsia are very sensitive to pitressin and pituitrin. A dose of pitressin which gives a negligible change in blood pressure of normal pregnant women also has no significant effect in pregnant patients diagnosed as having hypertensive disease. Such a dose given to the patient with preeclampsia, however, results in a marked rise in the blood pressure, a decrease in the urine volume output and subjective reactions. De Valera and Kellar[32] made similar observations but did not think that the results were consistent enough for differential diagnosis. Browne[15] extended these observations by showing that the preeclamptic's sensitivity to pitressin arises *de novo*. Early in pregnancy the patients reacted normally; with the appearance of preeclampsia the response became exaggerated. At follow-up study, the sensitivity disappeared.

II. *Cold pressor test.* Most of the studies of the cold pressor test in pregnancy have been concerned with the prediction of later development of toxemia. Some writers[28,99] have concluded that the test has no value in this re-

gard, while others[12,65,97], have thought that it has. Dieckmann, Michel and Woodruff[36] found exaggerated responses to the test in pregnant patients with hypertensive disease, while preeclamptic and eclamptic patients gave only small increases in the blood pressure. Bak[7] found minimal responses to the test during preeclampsia. Reid and Teel[99] did not find the test to be of any practical value in the differential diagnosis of the toxemias. Assali and Prystowsky[6] found that preeclamptics reacted no differently from normal pregnant patients.

III. *Tetraethylammonium chloride test.* Assali and his co-workers[3,4] have found that normal pregnant women respond to intravenous TEAC with marked drops in blood pressure, even to shock levels. Pregnant women with hypertensive disease also show considerable drops in the blood pressure. In contrast, patients with preeclampsia show only negligible decreases. Assali's work has been confirmed by Dumoulin[40], who noted, however, that some patients with mild preeclampsia did show marked falls in blood pressure. Govan *et al.*[47] confirmed Assali's findings in preeclampsia but some of their patients with essential hypertension failed to show blood pressure decreases with the drug. Werkö and Brody[123] report that TEAC often causes marked blood pressure drops in preeclampsia.

In establishing that the effect of TEAC on the blood pressure in pregnancy is through autonomic blockade, Assali *et al.*[4] compared the effect of high selective spinal anesthesia. The effect was very similar to that of TEAC and made the same differentiation between normal pregnancy, preeclampsia and hypertensive disease. Some clinicians have questioned Assali's finding that such selective spinal anesthesia does not affect preeclamptic hypertension, for continuous caudal or spinal anesthesia has been used in the treatment of preeclampsia and eclampsia, with marked reductions in the hypertension[78,124]. The disparity is only apparent, for Assali stated that the dosage of procaine used was so small as to affect only the naked vasoconstrictor and pain receptor fibers (*selective*); larger dosages of the agent produce muscular paralysis with consequent pooling and stagnation of blood in the flaccid areas.

IV. *Urate clearance.* Chesley and Williams[30] reported that the urate clearance in preeclampsia is depressed to a greater degree than are the simultaneous clearances of inulin and urea; published data of earlier workers also show this, although the fact had escaped attention. This points to an increased tubular reabsorption of urate from the glomerular filtrate. Seitchik[112] has confirmed the observation and put the same interpretation upon it. Chesley[23] has studied a large series of toxemic patients and found that the urate clearances usually accord with the clinical diagnosis. Nearly 90% of the patients diagnosed as having preeclampsia had depressed urate clearances and nearly 90% of the depressed clearances were found in patients with preeclampsia. A number of hypertensives were followed in pregnancy; they had normal clearances of urate and urea until rather late in pregnancy, when some showed a drop in the urate clearance which heralded the onset of the preeclamptic syndrome. This was interpreted as evidence that the exacerbation in hypertension and the appearance of proteinuria in such patients really is superimposed preeclampsia.

V. *Phospholipid/cholesterol ratio in plasma.* Boyd[11] differentiated true preeclampsia and eclampsia from the other toxemias on the basis of an elevated ratio of plasma phospholipid to total cholesterol. In normal pregnancy and

in about 75% of the patients classified as preeclampsia, the ratio averaged 1.14. In eclamptic and "literally preeclamptic" patients the ratio averaged 1.68. However, Mukherjee[86] found no significantly altered ratio of lipid phosphorus to cholesterol, although the ratio did tend to increase slightly in individuals whose preeclampsia or eclampsia was becoming worse.

VI. *Water excretion.* Clinicians long ago noted the tendency to oliguria in patients with severe toxemia. Janney and Walker[58] devised a water tolerance test and found that there is a considerable reduction in the rate of excretion of ingested water, by normal pregnant women. In women with toxemia the reduction is extreme. Odell *et al.*[88] infused 5% dextrose rapidly and found that patients with toxemia excreted water much more slowly than did normal pregnant patients; excretion is particularly retarded in preeclampsia. Dieckmann *et al.*[38] applied the Robinson, Kepler and Power test in a number of pregnant normal and toxemic patients. The patients were given 1200 cc. of water by mouth, between 7:00 and 7:45 a.m. Urines were then collected at hourly intervals from 8:00 a.m. up to and including noon. The test consists of two parts:

1. A comparison of the hourly urine volumes with the night urine volume (9 hours preceding the ingestion of water). If the volume of the largest hourly output is less than the night volume, the test is positive. (Originally the test was devised for the detection of Addison's disease and a positive response indicated the possible presence of the disease).

2. Calculation of the "water factor":

$$\text{Water factor} = \frac{\text{Urea in night urine}}{\text{Urea in plasma}} \times \frac{\text{Chloride in plasma}}{\text{Chloride in urine}} \times \frac{\text{Largest hourly vol.}}{\text{Night volume}}$$

In the test for Addison's disease, a water factor greater than 30 or any hourly output greater than the night volume excluded Addison's disease (in the absence of renal disease or pregnancy).

For the ratio of maximal hourly volume to night volume, Dieckmann *et al.* found abnormal responses, ante partum, in 33% of normal patients, 48% of patients with essential hypertension and 82% of those with preeclampsia. Post partum, about one-third of the women in each group gave abnormal responses. They wrote that their data had not been analyzed completely, "but it looks as if one could state that if a patient has a urinary output comparable to that found in essential hypertension, she does not have preeclampsia. However, if the output is decreased within the limits for preeclampsia, she might have either or both conditions."

The "water factor", in antepartum patients, averaged 194 ($\sigma = 288$) in essential hypertension and 24 ($\sigma = 36$) in preeclampsia. Post partum the means were 159 ($\sigma = 315$) and 99 ($\sigma = 200$), respectively.

Many investigators have reported the presence of antidiuretic activity in the urines of patients with toxemia. The validity of most of this work has been called into question by the recent demonstration by Krieger, Butler and Kilvington[64] that bacterial contamination of the preparations assayed is responsible for most of the antidiuretic activity induced in the test animals. On this basis they retract their own previous conclusion that toxemic patients often excrete an antidiuretic substance in the urine.

Ham and Landis[51] found increased amounts of an antidiuretic substance extractable from placentas of toxemic patients as compared to placentas of

normal cases. They showed that it was not the pituitary antidiuretic hormone, on the basis of its greater molecular size and its failure to stimulate chloruresis. Byrom[18] repeated the work with many more cases and failed to find a significant difference between normal and toxemic cases. Again, bacterial contamination may have been responsible for most of the antidiuretic activity. Chesley and McFaul[29] perfused cotyledons of surviving human placentas in Lindbergh pumps. When the cotyledons were perfused adequately, the perfusates had no antidiuretic activity. When they were perfused very slowly ("artificial placental ischemia") the perfusates usually had definite antidiuretic activity but did not stimulate chloride excretion. The sterile perfusates were concentrated in vacuum desiccators with no thought of keeping them sterile. However, the procedures were identical in all cases and the perfusates from the "ischemic" placentas were no more liable to contamination than were the control perfusates. This consideration probably also applies in many of the reported assays of normal versus toxemic patients' urines, although Krieger *et al.*[64] wrote that in their own original work the conditions were not identical in the collection and preservation of urines from normal and toxemic cases.

Chesley and Alter[26] gave repeated injections of *sterile* perfusates to rabbits and dogs. Perfusates from adequately perfused placentas had no discernible effect. The "ischemic" perfusates induced oliguria, and tremendous water retention as indicated by weight gain, edema, ascites and even hydrothorax. However the protein content of the ascitic fluid was high (1.7 to 4.1 gm. per 100 cc.) and there may have been a prerenal deviation of the water rather than a specific antidiuretic effect mediated in the renal tubules.

VII. *Saline tolerance test.* Dieckmann *et al.*[37] have proposed as a diagnostic test the rapid infusion (30 to 40 minutes) of a liter of 2.5% sodium chloride. The bladder is emptied 15 minutes after the end of the infusion and 2 1-hour urines are then collected and analyzed for sodium (or chloride). In 18 normal pregnant women, they found a mean urinary sodium concentration of 240 mEq./L. ($\sigma = 40$). In 28 pregnant women with hypertensive disease the mean was 196 ($\sigma = 52$) and in 20 women with preeclampsia the mean was 101 with a standard deviation of 65 mEq./L. They set the urinary sodium concentrations to be used in differential diagnosis as less than 144 mEq./L. for preeclampsia, 144 to 220 for hypertensive disease and over 220 for normal pregnancy. Also they postulate another group, "pseudopreeclampsia", in which the patients concentrate sodium better than do preeclamptics but not so well as the hypertensives; no concentration range is specified for this group.

It is interesting to note that the toxemic patients cover a continuous range below the normal dividing line of 220, and that the hypertensives do not concentrate sodium normally. On statistical grounds, the concentrations given as differentially diagnostic appear to be highly arbitrary and open to serious question. Patients concentrating urinary sodium to more than 144 mEq. are not preeclamptics by this definition. Yet the mean for all 20 preeclamptics is 101 with a standard deviation of 65. The cutoff point of 144 represents the mean plus 0.66σ and patients with any higher concentration are considered to have pseudopreeclampsia or hypertensive disease. In a normal distribution one would expect from the stated mean and standard deviation that 25% of preeclamptics would concentrate sodium to a higher level than 144. The mean

plus 2.5 σ would be 263, well above the dividing line for normal patients. It would appear from the large standard deviations that the test will not make a sharp differentiation of one group from another and the "pseudopreeclamptics", especially, look like gray cats. The dividing line below which preeclampsia is diagnosed represents approximately a 1:1 urine: plasma ratio, that is, no concentration of sodium by the kidney.

Dieckmann and his coworkers[34] have made extensive studies of salt tolerance in normal pregnant and toxic women, giving as much as 36 gm. of salt daily for many consecutive days. The normal patient in late pregnancy does not concentrate sodium in the urine so highly as she does in the nonpregnant state. Patients with hypertensive disease show no untoward effects from the high salt intake although, as noted, they do not concentrate it in the urine so well as do the normals. Patients diagnosed as preeclamptic differ in their response to high salt intake. About 20% of the "mild" preeclamptics are not affected adversely as judged by blood pressure response or degree of proteinuria; these patients concentrate sodium above 144 and are called "pseudopreeclamptics" by Dieckmann. The other 80% of preeclamptics often react to the salt with increased proteinuria, aggravated hypertension, progression of edema and the appearance or aggravation of symptoms.

The urines of eclamptic and severely preeclamptic patients long have been known to be low in chlorides and, presumably, in sodium. Dieckmann's observations on salt tolerance certainly indicate that many patients with toxemia do not concentrate sodium or chloride normally. Yet Assali *et al.*[5] have found that under osmotic (mannitol) diuresis the flow-load relation for both sodium and chloride is normal in preeclampsia. No consistent abnormality was found in the preeclamptic's renal handling of sodium. Of course such osmotic diuresis is an artificial condition, but in contrast to preeclamptics, edematous patients in cardiac failure or with cirrhosis often do show a considerably reduced sodium excretion per unit of total osmotic load.

Salt-retaining steroids have been found in the urines of toxemic patients. Tobian[120] reported that the excretion of formaldehydogenic corticoids is approximately doubled in normal pregnancy and increased still more in some edematous preeclamptics. Devis[33] has made similar observations, as have Parviainen *et al.*[94], Lloyd *et al.*[70], and Jailer[57]. Chart, Shipley and Gordon[21] did not find a significant increase in total corticosteroids but did observe urinary excretion of a salt-retaining substance in 7 women with toxemia. (The duration of "toxemia" in one of their cases was 5 months, which strongly suggests that this patient had hypertensive disease.) Venning *et al.*[121] also found the sodium-retaining steroid in all 43 cases of late toxemia studied. However, they found no correlation between the severity of "symptoms" and salt-retaining activity. Much work is in progress with this "electrocorticoid" which moves chromatographically with cortisone, but can be separated. It has been estimated to be 15 to 100 times as potent a sodium-retainer as desoxycorticosterone. What may be the same substance has been found in other syndromes associated with salt retention, for example, nephrosis[73].

VIII. *Hemoconcentration.* Dieckmann[34] has shown that hemoconcentration is characteristic of severe preeclampsia and eclampsia. It is seldom found in women with hypertensive disease, even with the syndrome called "superimposed preeclampsia". This is one of Dieckmann's chief reasons for

not accepting this commonly made diagnosis. Not only is there hemoconcentration in severe toxemia, but there are abrupt changes in its degree. The hematocrit, taken as inversely proportional to the plasma volume, varies markedly in severe toxemia.

Caton *et al.*[20] and Freis and Kenny[43] confirmed Dieckmann's[34] observation of a decreased plasma volume in preeclampsia and eclampsia and Chesley's[22] observation of an increase in "extracellular fluid" as approximated by the thiocyanate space. They calculated the ratios of extravascular thiocyanate space to plasma volume and found that the ratio tended to increase with increasingly severe preeclampsia.

The abrupt changes in plasma volume are unexplained. Speculatively, ferritin may play some role. Shorr and Zweifach[113] have found marked increases in both VEM and VDM in toxemia, but these vasoactive substances were noted to be in balance. A predominance of VDM (ferritin) would open the capillary bed widely and favor filtration over reabsorption, thus leading to hemoconcentration. Possibly ferritin is released in bursts, with later compensation by VEM. The presence of these substances in toxemia is rather puzzling in view of the normal blood flows to the kidney, liver and splanchnic area and skeletal muscles (see below). The release of these substances, in shock, apparently depends upon hypoxia in the sites of origin. There may be enzymatic disturbances in toxemia, despite the adequate blood supply.

IX. *Renal filtration fraction.* A fairly typical finding in essential hypertension is a decreased effective renal plasma flow with the glomerular filtration rate at or near the normal level. As a corollary, the proportion of perfusing plasma filtered through the glomerular capillaries as "preurine" is increased, that is, the filtration fraction $= \frac{\text{(Inulin clearance)}}{\text{(Diodrast clearance)}}$ is increased. In preeclampsia the filtration fraction is either normal or decreased. However, the determination of the inulin and Diodrast (or para-amino-hippurate) clearances is not likely to become a routine procedure for the differential diagnosis of the toxemias. Also, there is some evidence that pregnancy increases both the effective renal plasma flow and rate of glomerular filtration[24]; this also seems to happen in pregnant patients with hypertensive disease and the filtration fraction becomes more normal.

X. *Cardiac output.* Hamilton[52] has reported that in preeclampsia the cardiac output is considerably increased over that found in normal pregnancy. In pregnant women with uncomplicated hypertensive disease it is normal, but in all 9 hypertensives with superimposed preeclampsia studied, the cardiac output was increased as in preeclampsia. Werkö[122], using a dye method for the determination of the cardiac output, did not find an increase in preeclampsia (Hamilton used the cardiac catheterization method).

XI. *Enzymes.* Odell *et al.*[77,89], found the plasma levels of betaglucuronidase to be elevated in preeclampsia and originally suggested that this might be of value in differential diagnosis. However, according to Dieckmann[34], they subsequently decided that the change is not specific for preeclampsia.

Histaminase may be high, low, or normal in preeclampsia[1,61], as may pitocinase[91] and angiotonase[90].

XIII. *Plasma pentose.* Green *et al.*[48] found a significant rise in both the total and phosphorylated pentose of plasma in preeclampsia but not in hypertensive disease. The mean levels increased

with increasing severity of toxemia in the subgroups, but there was no good correlation in individual cases. They interpreted the elevated plasma pentose levels as indicating the loss of nucleotides from ischemic tissue (placenta?). However, Bonsnes and Stander[10] have determined plasma levels of nucleotides and found no significant changes in toxemia.

XIII. *Chorionic gonadotrophin.* The earlier work is reviewed by Smith and Smith[117]. Loraine[72] made quantitative determinations of serum levels and of 24-hour excretions of this hormone and found that high levels often (but not always) were present in severe preeclampsia. Most patients with mild preeclampsia and all with hypertensive disease had normal levels. Govan *et al.*[47] compared the gonadotrophin levels, response to tetraethylammonium bromide and a water excretion test. They found several combinations of test responses and not all preeclamptics had increased gonadotrophin.

XIV. *Electroencephalography.* Rosenbaum and Maltby[100] reported that 13 of 20 (65%) posteclamptic women had abnormal electroencephalograms at 1 week to 5 years after eclampsia. They suggested that the preeclamptic who goes on to convulsion might have a constitutional predisposition to convulsions, which is manifest in the EEG. Jost[59] found the pattern to be variable in 9 eclamptics and the recordings varied with the blood pressure; one patient had a normal tracing prior to convulsion. Schroeder[109] studied 18 eclamptics and found that the pattern was normal until the first convulsion. Berwind and Hann[9] found abnormal tracings in 2 posteclamptic women, but also in 4 of 12 preeclamptics. Parviainen *et al.*[95] found abnormal tracings in 5 of 6 severe preeclamptics, none of whom convulsed. Douglass *et al.*[39] followed unselected patients through pregnancy; ante partum, 57% had abnormal EEG patterns and one-third of all had the so-called convulsive pattern. No more patients in this group developed toxemia than in the group with normal patterns, and none of those with toxemia and convulsive EEG tracings did have a convulsion. Macintosh[80] found abnormal EEG patterns in 5 of 6 posteclamptic women.

XV. *Family history and personality traits.* McNeile and Page[79] confirmed many other writers in finding a high incidence (73% in only 11 cases) of positive family history of cardiovascular disease in women with essential hypertension. In contrast, such a family history was given by only 24% of their normal patients and 29% of their preeclamptic and eclamptic women. Barnes and Browne[8] determined blood pressures of 226 relatives of 129 patients with toxemia of pregnancy and of 66 relatives of 47 normal pregnant women. Except for patients with essential hypertension, there was no difference between toxemic and normal patients in the incidence of familial hypertension.

McNeile and Page[79] also assessed the personality traits of their patients, using the method outlined by Ayman. A very large proportion of the patients with essential hypertension were high-strung, excitable, nervous, shy, and so forth. In contrast, the patients with preeclampsia and eclampsia did not differ from the normal controls in the incidence of positive answers to the questions.

These approaches to the problem obviously cannot be applied to individual patients for the purpose of differential diagnosis. The marked differences between the hypertensives as a group and the acutely toxemic patients as a group do suggest that we are dealing with different diseases.

XVI. *Follow-up studies.* If all of the toxemias are but manifestations of hypertensive disease, then nearly all women having toxemia might be expected to develop hypertension if they live long enough. Nearly all women surviving eclampsia at the Margaret Hague Maternity Hospital have been reexamined periodically for the past 20 years[25]. Of 31 such women now aged 50 or more, 30, all but one, now have blood pressures of 140/90 or higher. All of the younger women show a steady increase in the incidence of such blood pressures with advancing age. If this level of blood pressure be taken as the standard for hypertension, then it would appear that perhaps all of the eclamptics are destined for hypertension. However, there is serious doubt that a blood pressure of 140/90 is abnormal in older women. Master, Dublin and Marks[84], from an extensive statistical study, have concluded that the upper limits of blood pressure increase progressively with age. By their criteria for the diagnosis of hypertension, only 10% of the posteclamptic women now have hypertension and there is no increase in the incidence with age. By their standards, the vast majority of eclamptics do not appear to be destined for hypertensive disease.

The Vascular Aspect. A popular concept of preeclampsia-eclampsia is that fundamentally it is a vascular disease. The suggestion was made by Volhard, many years ago, and was popularized in this country by Irving's 1936 paper entitled "The Vascular Aspect of Eclampsia"[56]. Hertig[53] subsequently suggested that the common denominator underlying the varied pathology of eclampsia is vascular spasm and that toxemia is an arteriolar disease. Many papers have described retinal arteriolar spasm in toxemia. Hallum[50] found such changes in nearly every patient who had a blood pressure of 150/100 or more for 2 days or longer; 41% showed arteriolar spasm with lower blood pressures. However, most writers have not found the changes so consistently, but all do agree that the spasm often can be seen. Also, the hypertension of preeclampsia very probably depends upon arteriolar constriction.

Before accepting vascular constriction as fundamental in the toxemic picture, however, 2 questions must be answered. Does it precede all other signs? Does it compromise the circulation, thus impairing organ and tissue function?

I. Rapid weight gain, representing water retention, is almost generally believed to be a frequent first sign of developing preeclampsia. This has not been rigorously established. Siddall and Mack[114] found that 45% of their nontoxemic women showed, at some time in the last 4 months of gestation, twice or more the average rate of weight gain. In reviewing records of preeclamptic patients one might, then, expect to find that nearly half had had a sudden spurt in weight gain at some time, perhaps preceding the clinical triad of hypertension, edema and proteinuria. Inasmuch as edema is one of the classic signs of preeclampsia, there is a predisposition to accept the rapid weight gain as the beginning of edema formation and a first sign of toxemia. While more than 50 papers have been published on weight gain in pregnancy, there seems to be none in which the data are presented or analyzed in such a manner as to prove what many regard as axiomatic.

Another approach to the problem of water retention as an early sign of toxemia has been the determination of thiocyanate spaces[22], once thought to approximate the extracellular water and now thought to parallel the sodium space (at least in most cases)[2,60]. Many patients who later developed pre-

eclampsia showed increases in the thiocyanate space before any other sign of toxemia.

The clinical consensus is that rapid weight gain may sometimes precede any evidence of vascular constriction; water retention, as judged from increases in the thiocyanate space also does so.

II. Smith and Smith[117] long ago found that an increased urinary excretion of chorionic gonadotrophin and decreased excretion of estrogen and progesterone metabolites often precede any other sign of developing preeclampsia, sometimes by several weeks. That is, these typical signs of preeclampsia precede detectable vascular constriction.

III. The urate clearance has been found to drop in incipient preeclampsia, before any signs of vascular constriction appear[23]. A more common observation (because of more cases studied) has been that the urate clearance remains low in those patients with "mild" preeclampsia who are clinically "cured" by treatment. All signs of vascular constriction disappear, but this characteristic renal finding of preeclampsia persists.

IV. There have been reported and the writer has seen cases of fatal eclampsia without hypertension. At necropsy the so-called characteristic lesions have been found in the liver. Without hypertension, it is doubtful that vascular constriction was prominent. Moreover, some eclamptics continue to have convulsions and show no sign of improvement when the blood pressure is maintained at normal levels by hypotensive drugs.

V. Brill *et al.*[13,14], have reported that the development of preeclampsia can be predicted with some accuracy through the detection of retinal arteriolar spasm by means of the flicker fusion threshold. The test is based upon the report of Krasno and Ivy[63]. They conceived that retinal arteriolar spasm should decrease the blood supply to the retina with a consequent diminution in visual acuity. In terms of the test, this would be manifested by a diminished perception of discrete, closely spaced light impulses, so that a flickering light would appear to be continuous at a lower than normal rate of flicker. Administration of a vasodilator (nitroglycerin) would increase the blood supply to the retina; in the subject with vasoconstriction nitroglycerin would improve the visual acuity but in the normal subject the retina would be flooded and the visual acuity decreased.

In the first place, the work of Krasno and Ivy has not been confirmed by investigators who have repeated it[42,101]. Thus the theoretic basis for the prediction of preeclampsia is shaky. In the second place, the work of Brill *et al.* has not been confirmed. Morris *et al.*[85], and Perl and Oper[96], found the test to have no predictive value for the development of preeclampsia.

To summarize, vascular constriction does not seem to be a primary factor in preeclampsia-eclampsia, for other abnormalities typical of the syndrome often precede it. Except in terminal cases, the available evidence seems to indicate that the vascular spasm does not interfere with the circulation. The hypertension which depends upon the constriction also compensates for it; one is the obverse and the other the reverse of the coin.

I. In a review of the literature on renal blood flow in toxemia, it was found that the blood flow to the kidney is, on the average, the same in eclampsia and preeclampsia as in normal women near term, although the range of variation is considerably increased[24]. Since then it has been noted that the renal blood flow may be somewhat

decreased in untreated preeclampsia and eclampsia[5,44,62].

II. McCall[74] has found that the cerebral blood flow is unaltered by pregnancy or preeclampsia. In eclampsia, there is a very slight decrease. Cerebral vascular resistance is increased in toxemia, but the hypertension compensates for this. Incidentally, McCall[75,76,119], found that the barbiturates decrease the cerebral blood flow and oxygen consumption. Morphine does not have such an effect and papaverine promptly and significantly improves the cerebral hemodynamics in toxemia of pregnancy.

III. Munnell and Taylor[87] found that pregnancy does not alter the liver blood flow. They studied very few cases of toxemia, but in those examined the liver blood flow was either normal or increased.

IV. Burt[17a] has reported that the blood flow in the forearm, probably representative of the musculoskeletal system, is augmented in pregnancy and increased still more in toxemia. She also found the skin blood flow to be increased in toxemia.

V. As was mentioned above, Hamilton[52] found the cardiac output to be increased in preeclampsia. This must mean that the circulation of blood is increased rather than decreased in the presence of preeclampsia.

VI. Browne[17] injected radioactive sodium into the maternal blood lake of the placenta, clapped a counter onto the abdomen and determined the rate of disappearance of radioactivity. From these determinations he calculated that the placental blood flow is decreased by about 2/3 in both preeclampsia and hypertensive disease.

In summary, the measurements of blood flow have covered most of the circulation without finding an area in which vascular constriction significantly decreases the rate of blood flow, with the possible exception of the placenta. The decreased flow in the placenta may depend upon some factor other than local arteriolar constriction, unless the spasm is much more marked here than in the rest of the body. Possibly, also, the vascular constriction interferes with the blood flow in the vasa vasorum and thus produces vascular damage.

Fluid Compartments and Body Water. Very little has been published on total body water and its compartmentation in pregnancy, although the work is going on apace in several laboratories. Haley and Woodbury[49], in a preliminary abstract, wrote that 3 normal pregnant women gained body water in the last weeks of pregnancy and that 4 of 5 lost water post partum. Their determinations were made by deuterium oxide dilution. Lambiotte-Escoffier *et al.*[66] determined total body water by antipyrine dilution in 2 normal and 7 preeclamptic women. They found an increase in the women with preeclampsia, both relatively and as shown by postpartum losses. Hutchinson *et al.*[55], using deuterium oxide, found that the water gain in pregnancy is roughly paralleled by gain in solids. They noted, as had Haley[49], that the rate of water turnover is unaltered in normal pregnancy; however the turnover rate is reduced in preeclampsia and accelerated in hypertensive disease.

Extracellular water probably has not been determined. Lambiotte-Escoffier *et al.*[66] determined the inulin space in one normal and 5 preeclamptic patients and found no increase. However it seems doubtful that their 5-hour infusion periods were long enough to establish equilibrium in edematous patients.

Ten to 15 years ago it was thought that the thiocyanate space approximated the extracellular volume, and the

writer determined this space in nearly 2500 normal and toxemic patients. This space is increased by an average of 6.3 liters during normal pregnancy and decreased by an average of 6.1 liters from labor to late puerperium. These measurements included the available water in the fetus, the placental and amniotic fluid water and the maternal blood water[22]. Caton *et al.*[20] found an average increase of 5.97 liters in the thiocyanate space during normal pregnancy. Freis and Kenny[43] confirmed the increase in preeclampsia. Friedman *et al.*[45] found comparable increases in the bromide space in normal pregnancy. These "obsolete" findings are mentioned because the thiocyanate space is very close to the sodium space[2,60], except in certain diseases[2]. However, the comparison has not been made in pregnancy. The sodium space is of particular interest in the toxemias and may have more significance, in this respect, than does the true extracellular space.

Carey[19] found increased sodium spaces in 4 women with preeclampsia. Cox and Chalmers[31] also found it to be increased in toxemia and further noted that the placental transfer of sodium is often decreased in preeclampsia. Lambiotte-Escoffier *et al.*[66] found the sodium space to be increased in preeclampsia, both relative to normal pregnancy and as judged by the postpartum decrease; the change in sodium space often was greater than that in the antipyrine space, and they suggested that some of the increased body sodium might be stored intracellularly.

Experimental Eclampsia. It is very difficult to decide upon any criteria for the diagnosis of eclampsia in animals. The disease is so variable in the human being and the triad of signs so nonspecific that hypertension, proteinuria and edema cannot be the sole standards. Most workers are agreed that there is no pathognomonic lesion in human eclampsia, which means that no rigid criterion can be set up on this basis. Also, eclampsia seems to be peculiar to the pregnant or puerperal woman and even if it were produced experimentally in some other animal it might not be recognized, because of a species difference. However, hope springs eternal and the quest goes on.

I. Smith and Smith[115,116] have partially separated a toxic euglobulin (possibly Menkin's necrosin) from menstrual discharge and endometrium, which they think may be the elusive eclamptic toxin. Injection of this substance into rats results in water retention with marked bloody edema around the site of injection. The rats develop bloody discharges from the nose and eyes. Some of the pathologic features of eclampsia were seen histologically.

II. Symeonidis[118] reported the production of an eclampsia-like syndrome in pregnant rats injected with progesterone. This is difficult to understand in the light of current thinking. However, repetition of the work by Hester *et al.*[54] did not confirm the original report.

III. Chesley and Alter[26] perfused surviving human placental cotyledons in the Lindbergh pump. With rapid perfusion, the perfusates had almost no discernible effect when given intravenously to rabbits and dogs, at 4-hour intervals and in large amounts. In contrast, relatively small amounts of perfusates obtained by very slow perfusion of the placenta (artificial ischemia) were toxic. The animals retained tremendous amounts of fluid and developed proteinuria. The rabbits developed mild hypertension and often died in convulsion. Blood pressures were not determined in the dogs, some of which died in coma. Several pathologists studied the tissue sections and their opinions ranged from "noth-

ing like eclampsia" to "it is eclampsia." No conclusion was drawn by the authors.

IV. Masson, Corcoran and Page (I.H.)[82,83] produced hypertension in rats by giving desoxycorticosterone (DCA) and drinking water containing salt. Injection of these rats with renin produced a syndrome resembling human toxemia of pregnancy. Page[92], has repeated the work and says that this is the closest approximation to toxemia of pregnancy which he has seen. He also found that, in contradistinction to renal hypertension, DCA hypertension is not alleviated by pregnancy in animals[93].

However, there are some observations which do not fit with the hypothesis that toxemia is "caused" in some comparable manner, although the addition of renin admittedly complicates interpretation.

A. Shorr and Zweifach[113] found marked, but balanced increases in VEM and VDM in human toxemia of pregnancy, as well as in essential hypertension and experimental renal hypertension (and a variety of other conditions). They found no such increase in DCA hypertension.

B. In essential hypertension and experimental renal hypertension Shorr *et al.* [68,125] describe a striking alteration in the capillary bed, with an increase in the number of capillaries and an increase in the sensitivity to topical epinephrin and injected VEM. Landesman *et al.*[67] describe some such changes in normal pregnancy, which seem to be exaggerated in toxemia, in the vascular bed of the bulbar conjunctiva. Such alterations do not occur in DCA hypertension.

C. Injections of pitressin into animal with DCA hypertension produce drops in blood pressure[46]. Patients with preeclampsia are very sensitive to pitressin (see above) and react with marked rises in blood pressure.

D. Dieckmann[34] has given DCA and salt daily for a week to patients with preeclampsia without any significant effect upon the hypertension, proteinuria or symptoms.

E. There is some doubt that the adrenal, or any other tissue, produces significant amounts of desoxycorticosterone.

V. Magara[81] prepared a water-soluble, alcohol-insoluble extract of placenta which gave a hyperergic reaction when injected into pregnant animals. There was evidence of vascular spasm; premature separation of the placenta occurred and lesions "coinciding" with those of eclampsia were produced in the uterus, liver, kidney and heart. Urine and blood of toxemic patients had the same effect upon pregnant animals.

VI. Seegal *et al.*[71,110,111] have done some fascinating work which may be of significance for our problem. They have found that placental tissue uniquely can be substituted for kidney tissue in the production of the Masugi nephritis. As a typical experiment, ground-up placental tissue (or, of course, kidney tissue) of the rat is injected intraperitoneally into rabbits over the course of weeks. The rabbits develop an antibody and when their serum is injected into rats a nephritis develops in a high percentage of cases. When given to pregnant rats the serum invariably result in abortion, but these authors have adduced some evidence that the pregnant animal is more susceptible to the nephrotoxic effect of the injections. They do not purport to have produced experimental toxemia.

VII. Lin[69] followed up Seegal's work by injecting female rats intraperitoneally with rat placenta suspensions. Five months later the rats were mated. Prior to pregnancy they had no pro-

teinuria (rats often do have), but developed it during pregnancy. In the data tabulated for 8 rats, the proteinuria was always present on the 6th day of gestation, the first day shown. Also, hypertension was found in the first third of pregnancy in 6 of the 8 tabulated; in 4, it was aggravated in the last third of pregnancy. All rats went to term. The consistent histologic finding was arteriolar sclerosis (which is not typical of eclampsia). No liver lesions were mentioned.

VIII. Schneider[102-107] repeated much of the earlier work in which animals were injected with placental extracts. In general, these extracts have no discernible effect unless given intravenously; by this route they often cause prompt death by fibrin deposition, especially in the lung vasculature. Sublethal doses often result in focal liver necrosis. Schneider has adduced evidence that the "toxin" is thromboplastin. The placenta and particularly the decidua are rich in thromboplastin, and Schneider has argued that autoextraction into the maternal circulation may account for some of the pathologic features of eclampsia.

Summary. Preeclampsia-eclampsia seems to be a different disease entity from essential hypertension. The various differential tests which have been proposed for diagnosis lack specificity probably because they all measure effects of the disease and the effects vary widely from case to case.

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PATHOLOGY AND BACTERIOLOGY

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BACTERIOSTATIC ACTION OF THE K VITAMINS*

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THE first part of this review is a summary of the main experimental data showing the bacteriostatic action of vitamin K and some of its analogues; the second part is an attempt to give an interpretation of this information.

A vitamin may be defined in a negative way by the consequences of its absence in a diet otherwise complete and balanced, that is to say by the avitaminosis which follows; a vitamin may be defined in a positive way by the prevention or the cure of these troubles by the use of chemically defined substances, which form a "family" of vitamins. The clinical manifestation of K avitaminosis is a hemorrhagic condition due to the decrease of the blood prothrombin level. This condition occurs in human beings, especially in the newborn infant, and in obstructive jaundice. The relationship of this avitaminosis to the clotting of blood led Dam to suggest the name of vitamin K (Koagulationvitamin) for the substance or substances present in extracts able to prevent or cure the hemorrhagic condition, and the properties of these substances show that they belong to the group of the fat-soluble vitamins.†

Several substances are now known to be able to prevent or cure the hemorrhagic condition by acting on the level of the prothrombin. All these substances are derivatives of the 1.4 naphthoquinone; some can be extracted from natural sources, others are only

*Lecture given at the Institute for Microbiology and Hygiene, University of Montreal November 18, 1953.

†For general information about vitamin K and K avitaminosis refer to:

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obtained by synthesis. Phtiocol or 2-methyl-3-hydroxy-1.4-naphthoquinone has been extracted from the human tubercle bacillus (Anderson and Newman[5]) and it has been synthesized by Anderson and Newman[6] and Fieser[28]; its antihemorrhagic power is low, about 1/500 of the antihemorrhagic power of vitamin K_1 (Almquist and Klose[1]). Vitamin K_1 has been isolated from alfalfa leaves (Dam *et al.*[24]); it is also a 2-methyl-1.4-naphthoquinone, but the carbon 3 bears a long aliphatic phytyl chain. Vitamin K_1 had been synthesized simultaneously, in 1939, by three groups of workers: Almquist and Klose[2], Fieser[25] and MacCorquodale *et al.*[52]; it is a 2-methyl-3-phytyl, 1.4-naphthoquinone (γ-phylloquinone). Vitamin K_2 has been extracted by McKee *et al.*[54,55] and Thayer[72] from putrefied fish meal. It has not yet been obtained by synthesis and its structure is not yet definitely known, and Fieser[30] believes it to be a 2.3-difarnesyl-1.4-naphthoquinone, but according to Binkley, McKee, Thayer and Doisy[14], and to Karrer and Epprecht[44], it might be a 2-methyl-3-difarnesyl-1.4-naphthoquinone. Other naphthoquinone derivatives isolated from vegetable sources have also an antihemorrhagic action: 3-hydroxy-1.4-naphthoquinone, "Lawsone" from *Lawsonia inermis* (Lythracoea), henna; 5-hydroxy-1.4-naphthoquinone, "Juglone", from the walnut; 2-methyl-hydroxy-1.4-naphthoquinone, "Plumagin", from *Plumbago officinalis* (Plumbaginacoea); "Phlorone", p-xyloquinone from beechwood tar also possesses a slight antihemorrhagic action (Ansbacher and Fernholz[8]).

Many artificial compounds related to vitamin K have been prepared with the special purpose of therapeutic use and to obtain more active substances which are soluble in water for intravenous use. The simplest synthetic substance is 2-methyl-1.4-naphthoquinone (Almquist and Klose[3]; Ansbacher and Fernholz[7]; Fieser[28]); called menaphtone in the British Pharmacopoeia and menadione in the U.S.A. Pharmacopoeia.

Among the numerous derivatives which have been prepared the most important are: esters of organic acids (diacetate, dipropionate, disuccinate); esters of mineral acids (phosphoric acid, sulfuric acid); addition compounds with sodium bisulphite; chlorhydrate of 4-amino-2-methyl 1-naphtol; dibenzoyl-sulfonic ester of the 2-methyl-1.4-naphthohydroquinone, and others[23]. The main points concerning the relation between the molecular structure and the antihemorrhagic property are an intact benzene ring and a 2-methyl group. The quinone structure is not essential, as hydroquinones are as active as quinones; the side chain in the 3-position can be eliminated without loss of activity and the quinone oxygen may be replaced by an amino or an aldehyde group (Fieser[29,31], Sjogren[69]).

On account of their chemical structure, K vitamins possess the bactericidal properties of the naphthoquinones and naphthohydroquinones and these properties have long been used in general disinfection or as therapeutic agents. Interest in the study of the bactericidal power of the quinones revived when it was shown that quinonic structure is present in some antibiotics. Thus according to Waksman and Woodruff[73] actinomycin A contains 10 to 12% quinones, although this amount does not account for the whole antibiotic power. Numerous quinonic substances have been shown to be antibiotics: fumigatin and spinulosin from *Aspergillus fumigatus* and *Penicillium spinulosum*, phoenicin from *P. phoeniceum; citrinin* from *P. citrinum* and *Asp. candidus;* crepin from *Crepis taraxacifolia*, and others; also see Ox-

ford[61], Oxford and Raistrick[62] and Waksman and Woodruff[73]. More recently a systematic study has been made of the pharmacological properties of about 300 naphthoquinone derivatives (Findlay[32]). These substances are strong inhibitors of the cellular respiration measured *in vitro* for yeast and red cells infected by *Plasmodium knowlesi* of the monkey, *Plasmodium lophurae* of the duck and some are also active against *Pl. cathamerium* of the canary. Naphthoquinones have antibiotic properties against numerous Gram-positive and Gram-negative germs: Staphylococcus, Streptococcus, Pneumococcus, *Bac. anthracis*, Brucella, Salmonella, Pasteurella, *Bac. subtilis*, *E. coli* and also against fungi such as *Asp. niger*, *Penicillium notatum* (Gonzalez[37]). Vitamin K does not seem to influence either growth or respiration of yeasts (Dam *et al.*[25]).

The strength of the antibiotic power varies very widely, according to the germ and the experimental conditions. The average concentration is 10 μg per cc.; Armstrong, Spink and Kahnke[10] found 2-methyl-1.4-naphthoquinone to have a bactericidal action against various strains of Streptococci, Staphylococci and Pneumococci whereas in the same concentration it is inactive against *E. coli*. Colwell and McCall[21] describe the bactericidal and bacteriostatic action of synthetic vitamin K and some analogues for *E. coli*, *St. aureus*, *Asperg. niger*. Tavoni[71] has studied the bactericidal and bacteriostatic action of menadione against numerous micro-organisms: *Bac. anthracis*, *B. suipesticus*, *Brucella militensis*, *Br. abortus*, *Br. avisepticus*, *Str. mastitidis*, *E. coli*, *Staph. aureus*. Infrabactericidal concentrations may induce mutations; Colwell[20] obtained reversible mutants of *E. coli*, having lost the capacity to ferment mannitol; simultaneously Clark, Wyss and Stone[19] obtained mutants of *Micr. pyogenes* resistant to penicillin by action of menadione at a low concentration: 0.5 to 6.0 $\times$ 10^{-6}; the property being retained after repeated subcultures on agar. This result is to be compared with the finding of Pratt *et al.*[66] that the bacteriostatic action of vitamin K_5 (hydrochlorate of 2-methyl-4-amino-1-naphthol) plus penicillin against *E. coli*, *Staph. aureus and Proteus vulgaris* is higher than the sum of the action of each single substance. Some experiments concern *Mycobacterium tuberculosis*: the growth of H. 37 Rv is inhibited by 2-methyl-1.4-naphthoquinone and phthiocol; active doses are quite high: 4.0 to 5.0 mg. per 100 cc. (Heise and Steenken[39]). Lloyd and Middlebrook[50], and Inland[43] have studied numerous naphthoquinones and found a wide variation of activity on tubercle bacilli according to their molecular structure. Kimler[45] set 1 μg/cc. as the minimum concentration of C1H-4-amino-2-methyl-1-naphthol to reduce the growth of *M. tuberculosis* H. 37 Rv by 50% when cultivated on Youman's medium.

Panisset, Simonnet and Dobija[64] reinvestigated the bacteriostatic action of menadione and some derivatives *in vitro* with the view to an investigation in the living animal. At first they determined the bacteriostatic power of menadione for B.C.G. to lie between 1 and 10 μg per cc. and a 7 days' old culture of B.C.G. in Dubos' medium containing 1 μg menadione per cc. when subcultured in fresh medium shows a granular aspect. B.C.G. resistance to PAS, measured by the Herrold's egg technique, was not modified by menadione and remained at the level of 0.05 μg/cc.

Again no variation in the resistance was noted even after four transfers in Dubos' medium containing menadione at concentrations varying from 0.1 to

1.0 μg. Suspensions of *Myc. tuberculosis* var. B.C.G. (1.0 mg./cc.) received amounts of menadione ranging from 0.1 mg. to 1.0 mg. per cc. to 0.5 cc. was subcultured into 9.5 cc. of Dubos' medium after 30 min., 90 min., 9 hrs., 16 hrs., 90 hrs., by which it was shown menadione is bactericidal after a contact of more than 90 min. and less than 9 hrs. at the concentration 1 part per 1000 and after more than 16 hrs. and less than 90 hrs. at the concentration 1 part per 10,000. The samples which were in contact with menadione at 1×10^{-4} during 16 hrs. and those which were in contact with menadione at 1×10^{-3} during 90 min., that is, at concentrations which are not bactericidal, became resistant to more than 10 mg. PAS and this property is stable after subcultures in fresh Dubos' medium. It is permissible to think that something like a mutation occurred, characterized by a diminution of the low virulence of the B.C.G.

In their *in vivo* experiments, Panisset, Simonnet and Dobija inoculated mice of C.B.A. strain by the intracerebral route with 0.069 mg. *Myc. tuberculosis var. hominis* strain H. 37 Rv. Animals then received subcutaneously twice a week 10 μg. menadione per gm. of live weight, that is, 200 μg. menadione per animal or 2.4 μg. menadione for the 6 weeks of the experiment. The course of mortality is summarized as follows:

	14th day	*28th day*	*45th day*
Without menadione:			
Dead	3	6°	8
Living	7	4	1
With menadione:			
Dead	0	1°°	2
Living	10	9	7

°One mouse sacrificed the 28th day: nodular lesions containing acid-fast bacilli in the lungs.

°°One mouse sacrificed the 28th day: no macroscopic lesions. acid-fast bacilli present in the lungs.

Another experiment was performed with the hydrosoluble vitamin K_1. Mice of the R.A.P. strain were inoculated by intracerebral route with 0.05 mg. *Myc. tuberculosis var. bovine*, Ravenel strain; 25 animals were used as controls, a second group of 25 mice received subcutaneously twice a week 500 μg. Synkavite, a total of 3.5 mg. per mouse; a third lot received 250 μg. per day, that is, 1.75 mg. per mouse. The evolution of the infection is summarized in the following table:

	Mortality %
14th day	
control	68
lot 1	36
lot 2	56
28th day	
control	80
lot 1	54
lot 2	84

Lungs of the controls show confluent tuberculous lesions which on microscopical examination show large necrotic zones involving the exudative cells and pulmonary parenchyma. In the treated animals the lesions are scarce, small, isolated nodules, not more than 8 for one lung, and microscopically these are small proliferative lesions, with congestion, numerous macrophages and fibrosis. The conclusion is that K vitamins exert a protective action against a gross tuberculosis infection but that menadione (the liposoluble form) is more potent than the hydrosoluble preparation, although both substances possess the same antihemorrhagic power.

This observation is to be compared with the results obtained by Levaditi *et al.*[49] with the dibenzoyl sulfonic ester of the 2-methyl-1.4-naphthohydroquinone (Levaditi, Vaisman and Chaigneau[49]). Mice were inoculated with *Myc. tuberculosis* H 37 Rv; one group received each day, first 5 mg., then 2.5 mg. of vitamin K, amounting

to 107.7 mg. for each mouse. Mortality from the 24th to the 37th day was 85 per 100 for the controls and 75 per 100 for the treated. The microscopic lesions in the lungs were slightly more severe for the controls than for the treated animals, but virulent renal lesions were noted in the latter. The authors conclude that vitamin K has no influence on the evolution of the experimental infection. The difference noted between the two groups of animals is of the same order as was observed by Panisset, Simonnet and Dobija with the hydrosoluble vitamin K preparation, but in Levaditi's experiment severe renal lesions are encountered in the treated animals. One may be surprised by the very high dose of vitamin K used by Levaditi as 2.5 mg. per day corresponds in mice to 125 mg. per kg. We do not know the LD_{50} of the preparation used but, according to the toxicity of other preparations (LD_{50}:750 mg./kg.) it seems to be very high and too close to the lethal dose. In the experiments of Panisset *et al.* the doses were 10 mg./kg. for menadione and 3.5 and 7 mg./kg. for the hydrosoluble preparation. The oral LD_{50} for mice for 2-methyl-1.4-naphthoquinone is approximately 500 mg. per kg. (Molitor and Robinson[59]).

From these experiments we reach the conclusion that vitamin K exerts a tuberculostatic action. This conclusion may be compared with the results obtained by Merklen[57] in the treatment of leprosy, whose results are summarized as follows: "Henceforth results obtained not only in leprosy reactions but also against other manifestations of lepra, namely nervous lesions against which sulfones are useless, lead to the statement that vitamin K derivatives are at least an important adjuvant in the treatment of lepra and that they should be frequently recommended".

Discussion and Interpretation. Experimental facts concerning the antibacterial properties of vitamin K are numerous and they are often contradictory. In order to try to give an explanation and set up a working hypothesis we shall consider the results obtained *in vitro* and those obtained in the living animal.

1. IN VITRO EXPERIMENTS. All naphthoquinones are not inhibitory. Phthiocol as well as 2-methyl-1.4-naphthoquinone stimulate the growth of *Myc. phlei and Myc. paratuberculosis* (Woolley and McCarter[78]); disuccinate of methyl naphthohydroquinone stimulates the growth of *E. coli* (Schmidt and Busing[67]), but these facts, especially those concerning the stimulation of *Myc. paratuberculosis*, have not been entirely confirmed, the extract being more active than the amount of phthiocol it contains. A question arises: are these growth stimulating properties to be associated with the ability of these microbes to elaborate phthiocol? It is well known that various kinds of Mycobacterium, cultivated on artificial media, synthesize phthiocol; *E. coli* forms vitamin K_2 in fish meal and in the digestive tract and also in artificial media (Dam[22], Almquist[4]).

What role do these substances play in the metabolism of the microbes? Are they useful metabolites or waste products? Do the germs against which naphthoquinones are inhibitory elaborate them? The ability to synthesize vitamin K is not uniformly found in microorganisms. *E. Coli* elaborates high quantities of vitamin K: 150 to 200 μg. per gm. *Bact. bifidum, Staph. faecium, Microb. lacticum, Bac. brevis* are less potent; some others, such as *Pseudomonas aeruginosa, Lactob. acidophilus* and yeasts do not elaborate any vitamin K (van Lanen and Tanner[46]).

But when naphthoquinones and naphthohydroquinones are inhibitory, important differences are found in the

intensity of their action and there is variation according to the kind of vitamin K acting on the same microorganism. The following example is taken from the work of Atkins and Ward[11] on *Staph. aureus*.

	Concentration						
	4,000	*8,000*	*16,000*	*32,000*	*64,000*	*128,000*	*256,000*
2-methyl-1.4 naphthoquinone	−	−	−	−	−	−	+
2-methyl-1.4 naphthoquinone diacetate	+	+	+	+	+	+	+
Tetrasodium salt of the diphosphoris ester of naphthoquinone	+	+	+	+	+	+	+
Disuccinate of 2-methyl 1.4 naphthoquinone	−	−	−	−	−	±	+
2-methyl-1.3-hydroxy 4-naphthoquinone (phthiocol)	−	−	+	+	+	+	+
2 methyl 1.4 naphthoquinone 2:3 oxide	−	−	−	−	−	±	+

In the case of *Myc. tuberculosis*, Inland[43] sets the inhibitory dose at 3×10^{-6} with hydrochloride of 4-amino-2-methyl 1-naphthol and at 166×10^{-6} for the tetrasodium salt of the diphosphoric ester of 2-methyl-1.4-naphthoquinone. Kimler[45] finds differences of the same order and we have noted variations of this magnitude with *Myc. tuberculosis* (*see above*). If the lack of inhibitory action alone is considered, the nature of vitamin K may be the cause of the difference of activity. Combinations with acetic, sulfuric or phosphoric acid are perhaps devoid of action because the microbe is unable to hydrolyse it. This hypothesis is supported by the fact that the disuccinate which hydrolyses spontaneously in water is active, whereas the diphosphate becomes active only when it has been hydrolysed by a phosphatase (Atkins and Ward[11]).

2. INHIBITORY ACTION IN RELATION TO THE GERM. Disuccinate of methylnaphthoquinone at the concentration of 1 part in 6,400 inhibits the development of *Staph. aureus* (the minimum dose being 1 part in 64,000) but it is inactive at the same concentration against *E. coli*. The same substance may be active against some strains and inactive against others: such is the case with strains of *Str. viridans* and *Str. faecalis*, and furthermore *B. subtilis var. Marburg* is inhibited, while *B. subtilis var. 1* is not inhibited. It is to be noted that Gram-positive germs are more sensitive than the Gram-negative ones. One may not be surprised by these differences as they are to be found in the action of other antibacterial substances.

The influence of the composition of the culture medium must also be taken into account. Generally speaking, the antibacterial action is less marked in common broth than in synthetic media (Colwell and McCall[21], Shwarzman[68], Woolley[77]) and it is well-known that the antiseptic action of quinones is inhibited by blood serum and peptones (Morgan and Cooper[60]). In this case again we meet with a property which occurs with antibiotics. Results concerning the mechanism of the inhibitory action of quinones *in vitro* against microbes, moulds and animal parasites may be summarized (Hoffman-Ostenhof[41,42]) by saying that quinones are able to give, with their reduction products the hydroquinones through the intermediary stage of semiquinones or quinhydrones, systems of oxydo-reduction which have well defined potentials

(Fieser and Fieser[31], McCawley and Gurchot[53]). The quinones may behave as hydrogen acceptors and the hydroquinones as hydrogen donors, able to compete with enzymatic systems which take part in oxydo-reduction processes (Page and Robinson[63]). As a matter of fact antihemorrhagic substances inhibit cellular respiration of *P. knowlesi* (Ball[13], Wendell[75]) and the *in vitro* glycolysis of *Schistosoma mansoni* (Buding *et al.*[15]); they are also inhibitory for the succinic dehydrase (Ball[13], Potter and Dubois[65], Wieland[76]). A process of this kind probably explains the inhibition by vitamin K of lactic acid formation in saliva containing dextrose. This property has led some to confer on vitamin K a protective action against dental caries (Armstrong and Knutson[9], Calandra, Fancher and Fosdick[16], Fosdick, Fancher and Calandra[33]). A similar explanation can be given of the action of vitamin K on respiration and photosynthesis in various algae: stimulation at low concentrations, inhibition at high concentrations (Gaffron[35]); and of the inhibition of mitosis in the egg of Tubifex (Lehman[47]) perhaps also of the polyploidic action described by Havas[38].

Another kind of explanation may be found, in that quinones as well as the non-saturated derived acetones and lactones can give additional products with -SH groups (Atkinson and Stanley[12], Cavallito[17], Cavallito and Bailey[18], Colwell and McCall[21], Geiger[36], Hickey[40], Muir and Valley[58]). In fact, the antibacterial action is often suppressed when the medium is rich in thiol containing compounds. For instance, the action of 2-methyl-1.4-naphthoquinone and 2-methyl-1.3-chloro-1.4-naphthoquinone is suppressed by cystein or thioglycolic acid, whereas the activity of 2-methyl-3-methoxy-1.4-naphthoquinone is not altered. The quinones have also the property of giving additional products with free amino radicles. This property has been used for a long time in the tanning power of benzoquinone and it may intervene in modifying the surface properties of microorganisms. It is probably also correlated with the fact that naphthoquinones give in the blood nondialyzable compounds less active on the respiration of infected red cells than pure naphthoquinones.

IN VIVO ACTION. *Antihemorrhagic action.* The absence of vitamin K leads to hypothrombinemia, but what role does vitamin K play in the elaboration of the glycoprotein prothrombin? The first point of importance is to ascertain if vitamin K is a constituent of prothrombin. Against this hypothesis it may be argued that animals deprived of vitamin K are not protected when they receive prothrombin in their food. It can be said on behalf of the hypothesis that peptic digestion of prothrombin leads to products which give characteristic color reactions of quinones. An interesting working hypothesis advanced by Lyons[51] is mainly based upon the property of naphthoquinones to combine with -SH radicles of the proteins. Thrombin is made up of two active components, thrombin A and thrombin B, neither of which alone will cause the coagulation of fibrinogen, although a mixture of both components will do so. Coagulation proceeds in two steps: Thrombin A reacts with fibrinogen liberating thiol groups (-SH) to form an intermediate, fibrinogen B, between fibrinogen and fibrin. Fibrinogen B is transformed into a fibrin gel either by thrombin B or by small amounts (1 μg.) vitamin K. This denaturation process which results in coagulation is due to the oxidation of -SH radicles into disulfure links -S-S-. This hypothesis has been criticized on experimental grounds (Dam[23], p. 34) but it deserves new investigation.

Concerning the mechanism of the tuberculostatic action *in vivo*, it may be admitted that it is similar to the tuberculostatic action *in vitro*, but such an hypothesis must take into account not only the competition between microbes and vitamin K but also the competition between vitamin K and the constituents of tissues and humors. This phenomenon which opposes organotropic and parasitotropic action is often encountered in pharmacology and is fundamental in chemotherapy. We can say very little about naphthoquinones in this connection. Perhaps intermediate substances are elaborated which are more active and more specific than the original substance.

Another hypothesis which does not exclude the former is the action of vitamin K on the organism "terrain" and the experiments of Tamburino[70] are interesting in this connection. Vitamin K (menadione) at high doses, 4.5 to 8.0 mg. for 7 to 30 days, causes a hypertrophy of the hypophysis due to the increase in number of eosinophilic cells which elaborate the somatotropic hormone. This reaction of the hypophysis is to be compared with the results obtained by Lemonde, Panisset, Dobija and Selye[48] concerning the protective action of somatotrophin against the tuberculosis infection in the rat sensitized by cortisone.

Concerning the correlation between the antihemorrhagic and the antibacterial effect it may be said on qualitative grounds that the comparison of the range of chemical structure to both properties does not show an exact superposition: all antihemorrhagic naphthoquinones do not exert an antibacterial action and conversely some antibacterial naphthoquinones are not antihemorrhagic (Armstrong and Knutson[9], Armstrong *et al.*[10]). On quantitative grounds the comparison is difficult, owing to differences in the estimation of the antibacterial activity. At present it is not possible to accept a parallelism between both activities, but it is permissible to admit the reality of a common field of structural activity, represented by the molecular structure of 2-methyl-1.4 naphthoquinone, and, more specifically, the property of the structure to compete with thiol radicles.

On experimental grounds it would be important to study again in the case of well defined strains of certain types of germ the bacteriostatic or bactericidal action according to the composition of the medium; namely, concerning the -SH and amino groups, the redox potential, and to investigate by cytochemical techniques the modifications of the structure of the bacteria. *In vivo* researches should include the treatment of less acute infections and the association of naphthoquinones with other tuberculostatic drugs.

However it may be, investigations concerning the antibacterial action of naphthoquinones raise interesting problems of bacterial physiology. They indicate the need to take into account in the evolution of an infection the interaction of the infectious agent with the host organism itself and they show how important it is to locate the basis of complex biological reactions in chemical and physiochemical processes. They also draw attention to a group of substances whose chemotherapeutic exploration is far from complete, as Fox[34] recently pointed out: "It is to be expected then that many of the compounds discussed here will in time be only of academic, or at most, historic interest. But that is not necessarily the full measure of their importance. To the chemist, at least these overt failures may provide the stimuli and the points of departure for further and possibly more successful research. The distinct but relatively inadequate activity of 3-

amino-isonicotinic acid proved to be an important stimulus to the discovery of isonicotinyl hydrazine. . . . The chemotherapy of tuberculosis in the future will probably involve a combination of two or more drugs, each of which will attack the tubercule bacillus via a different route, so that clinical arrest (if not sterilization) can be obtained before the emergence of resistant strains".

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PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF FEBRUARY 16, 1954

A Sensitive Spectrophotometric Method for Recording Enzyme Reactions in Cell Suspensions, Muscle and Nerve. BRITTON CHANCE, D.Sc., and C. M. CONNELLY, PH.D. (Johnson Research Foundation, University of Pennsylvania, and Jenkins Laboratory of Biophysics, Johns Hopkins University). The sensitive and rapid spectrophotometric methods used to obtain quantitative results on the steady-state properties of tissue homogenates and suspensions of single-cell organisms have been improved so that they can be applied to the study of the respiratory pigments of muscle and nerve. A sensitive recording spectrophotometer plots directly the difference of absorption between a pair of frog sartorius muscles, one aerobic, the other anaerobic. When the erythrocytes have been removed by perfusion, the absorption bands corresponding to reduced pyridine nucleotide, cytochrome, and flavoprotein are recorded with a 1-mm. thickness of tissues. Kinetic studies of spectroscopic effects related to activity are carried out in a flow chamber that encloses one sartorius muscle or four nerves between thin perforated sheets of lucite 60 mm.^{2} in window area. The optical path is 0.8 mm. The tissue is continuously bathed in Ringer's solution containing oxygen, nitrogen, or inhibitors. Artifacts are minimized by using a double beam spectrophotometer that flickers upon the tissue light of two adjacent wavelengths and records only the alternating component of the photocurrent. Wavelengths of 340 and 386 mμ are used in the recording of changes in the level of reduced pyridine nucleotides. The usual artifact, at an amplifier band width of 3.2 cps., caused by contraction of the muscle is less than 3% of the total deflection corresponding to the difference between the fully oxidized and fully reduced states of the muscle. The course of reduction of pyridine nucleotide in a nitrogenated muscle can readily be followed during tetanic stimulation or during a series of twitches. Smaller rapid changes in the level of reduced pyridine nucleotides caused by stimulation of aerobic muscle can be measured and may reflect the kinetics of rapid biochemical processes more intimately related to muscular contraction.

Spectrophotometrically Measured Changes in Concentrations of Reduced Pyridine Nucleotides in Resting and Active Frog Muscle and Nerve. C. M. CONNELLY, PH.D., and BRITTON CHANCE, D.Sc. (Jenkins Laboratory of Biophysics, Johns Hopkins University and Johnson Research Foundation, University of Pennsylvania). The difference between absorption at 340 mμ and that at 386 mμ is recorded automatically (see preceding abstract) and is interpreted as reduced pyridine nucleotide (RPN) using a molar extinction coefficient of 6×10^3 per centimeter path. RPN increases during anaerobiosis, rapidly during a first phase of 5 to 10 minutes, then more slowly and approximately exponentially during a second phase of 1½ to 7 hours at 26°. Total increases are 50 to 150 μM (micromoles per kilo wet

weight) in muscle and 30 to 40 μM in nerve. Rates of endogenous reduction during phase one are 0.05 to 0.25 μM/sec. in muscle, about 0.05 μM/sec. in nerve; in early phase two the rates are 0.1 to 0.2 as large. Stimulation of muscle (20/sec.) in N_2 increases RPN production to 4 μM/sec. Stimulation of nerve (100/sec.) hastens reduction by a factor 1 to 2. Some inhibitors cause large changes in the steady-state RPN level aerobically; in resting muscle, 1 to 5 mM iodoacetate or 1 to 2 mM hydroxylamine produces oxidation of 20 to 50 μM. Hydroxylamine does not interfere with function, but as a result of activity (2 min., 1/sec.) the steady-state RPN level increases by 150 to 200 μM. In nerve, hydroxylamine (1 to 2 mM) produces RPN oxidation of 10 to 20 μM, followed spontaneously by a reduction of 40 to 60 μM in 2 to 3 hours, the nerve remaining functional. In aerobic muscle at 7° one twitch produces 3 μM RPN oxidation; continuous stimulation (2/sec.) produces 35 μM total oxidation, maximum rate 7 μM/sec. Comparable stimulation of hydroxylamine treated muscle (with largely reduced PN) causes 100 μM total oxidation, maximum rate 2 μM/sec. Stimulation of fresh, thoroughly oxygenated muscle at 26° usually produces an oxidation of RPN, as large as 10 μM in some experiments. Stimulation of aerobic, uninhibited nerve (7 min., 100/sec.) causes no measurable (<1 μM) change in RPN at 26° or at 7°; comparable stimulation in hydroxylamine causes RPN oxidation of 5 to 10 μM. Thus, in normal muscle and in inhibited muscle and nerve we are able to demonstrate that functional activity results in oxidation of RPN, followed by recovery to the steady-state characteristic of the system at rest. These changes may find explanation in the observation of Chance and Williams that addition of adenosine diphosphate to metabolizing rat-liver mitochondria also produces a transient oxidation of RPN.

Variations in Alveolar R.Q. During Nembutal Anesthesia. AARON A. BECHTEL, A.B., (Dept. of Physiology, Hahnemann Medical College). In respiratory depression by Nembutal, respiratory exchange takes place at tension levels progressively displaced upward (from about 40 mm.) along the CO_2 dissociation curve and downward (from about 105 mm.) along the O_2 dissociation curve. The slope of the O_2 curve increases rapidly as tension decreases, and though the CO_2 curve is nearly linear in the physiological range, what change in slope exists is qualitatively similar to the O_2 curve above about 30 mm. It appears that the changes in slopes of the two curves describe the changes in gas transfer across the respiratory membranes, in units of volume per mm. of pressure change. With deepening respiratory depression, such change in slope as the CO_2 curve shows is negative, while the slope of the O_2 curve increases at an increasing rate as the O_2 tension falls. With numerator diminishing and denominator increasing, the R.Q. decreases. The increase in the denominator of the R.Q. does not, of course, mean an increase in volume transfer of O_2 from lungs to blood per unit time. There is, however, an actual decrease in the respiratory output of CO_2 due to the elevated alveolar pCO_2 following decrease in the alveolar ventilation. Blood CO_2 content rises; CO_2 retention occurs. In recovery these trends are reversed. However, pO_2 and with it the R.Q. may begin to rise while CO_2 is still piling up in the blood. (As long as the R.Q. is below the metabolic exchange ratio "CO_2 retention" may continue.) But as exchange takes place progressively higher on

the O_2 curve, the R.Q. increases until the slope of the O_2 curve becomes virtually linear in the region above 100 mm., when the R.Q. tends to level off. The excess CO_2 stored in the blood and in the region above 100 mm., when the R.Q. tends to level off. The excess CO_2 stored in the blood and other compartments during the period of ventilatory depression may continue to be "blown off" for several hours after the alveolar pO_2 and R.Q. have "leveled off".

Measurement of the Rate of Gastric Emptying in Man as Determined by the Clearance of a Radioactive Colloid (AgI^{131}): Normal Values, Effect of Urecholine Chloride and Morphine Sulfate. RICHARD L. WECHSLER and JAMES L. A. ROTH. (Departments of Gastroenterology, Physiology and Pharmacology, Graduate School of Medicine, University of Pennsylvania). A quantitative method for measuring continuously the rate of gastric emptying with minimal disturbance of normal function has been developed. Fifty μc of I^{131} in the form of a silver iodide colloid was suspended in 500 cc. of a standard pectin meal. The patient was in the supine position during the entire study. With the exception of the gastric area, which had been located previously radiologically, the entire abdomen was shielded by lead 4 inches thick. A scintillation counter was placed over the stomach at least 75 cm. above the anterior abdominal wall. Counts were recorded at one-minute intervals until a final plateau was reached. Counts per minute less final background were plotted semilogarithmically against time; a straight line resulted. The slope of this line yields a value for k, which represents the rate of emptying or clearance of the pectin meal from the stomach. Methods for minimizing possible sources of error, such as presence of small bowel loops behind the stomach, changes in the position of the stomach, absorption of the AgI colloid, and the volume of gastric residue after the plateau is reached, will be discussed. The exponential form of the results indicates that the amount of the meal emptied per unit time is a constant fraction of the volume of the meal remaining in the stomach. Fourteen determinations were carried out on 9 healthy young men. The mean value for the k of this group was 0.058 ± 0.0031 (S.E.). Results of studies with subcutaneous urecholine chloride (10 mg.) and morphine sulfate (10 mg.) will be reported.

BOOK REVIEWS AND NOTICES

RISIKO UND KOSTEN IN DER KRANKENPFLEGEVERSICHERUNG MIT BESONDERER BERÜCKSICHTIGUNG. By DR. ALFRED J. HOSCH. Pp. 127. Bern: A. Francke Ag. Verlag, 1953. Price, 12 Swiss fr.

THIS is a statistical review of the risk and cost of insurance for the care of the sick that belong to the "Krankenkassen" of Switzerland. Tables therein are extensive and numerous and could be compared with corresponding tables as determined by American insurance companies and like organizations (for instance, the "Blue Cross"). For such purposes the brochure would no doubt be instructive. However, the differences in social and economic conditions and the difference in purchasing power of the respective monetary units in Switzerland and the United States should be considered.

According to the text, there is an objective risk on the part of the companies, this dealing with the normal likelihood of illness in the insured, and of subjective risk, which is affected by the personalities of the insured. The analyses as set forth in the tables seem to be thorough. M. M.

ROENTGEN DIAGNOSIS OF THE HEART AND GREAT VESSELS. By ERICH ZDANSKY, M.D., Professor of Roentgenology, University of Vienna. Translated by LINN J. BOYD, M.D., F.A.C.P., Professor and Director of Medicine, New York Medical College. 1st American ed., new enlarged revision. Pp. 500; 334 ills., 5 in color. New York: Grune & Stratton, 1953. Price, $15.50.

CARDIOVASCULAR roentgenology has been recognized for many years as an essential part of the examination of every patient with disease of the heart or great vessels. With the development of newer techniques of examination, and as a result of the greater need for diagnostic exactitude in those cases being considered for surgery, the magnitude of the contribution made by cardiovascular roentgenology has been enhanced even further. Most cardiologists and many internists have recognized the value of being experts themselves at the techniques of cardiovascular fluoroscopy since they, rather than roentgenologists, are the ones who see cases in their entirety and are better able thus to correlate the findings with the pathophysiology of any particular case. They recognize also their role in contributing to the interpretation of angiocardiograms and other techniques available to the roentgenologist. The need for an authoritative, lucid, up-to-date text is, therefore, great, and the appearance of this translation of Dr. Zdansky's book should be welcomed by a host of physicians who are striving to improve their diagnostic acumen in a day when the result is so likely to be productive in a practical manner. Dr. Zdansky is recognized the world over as one of the leading authorities on this entire subject, but, formerly, his writings were available only in German. The selection of Dr. Boyd as a translator was a wise one since he is an internist with a special interest in cardiology.

The reader will find this volume well worth many hours of study. It is a magnificent exposition of the subject and one that can be used by the cardiologist and internist both in a didactic manner and as a reference book. Two very minor drawbacks are, first, an unnecessary retention of some of the German idioms (for example, the overuse of the words "precise" and "precisely") and, second, a failure by the publishers to make use of the magnificent German techniques for Roentgen-ray reproduction. But the clarity of the very large number of excellent drawings is such as to far outweigh such drawbacks. Some of these drawings are in color, and this provides an elucidation of three dimensional relationships in a fashion not otherwise possible. The material contained in the book is very much up-to-date, and there has been included an extensive bibliography. T. D.

THE PSYCHOSOMATIC CONCEPT IN PSYCHOANALYSIS. Edited by FELIX DEUTSCH, M.D. Pp. 182. New York: International Universities Press, Inc., 1953. Price, $4.00.

THIS book is a compilation of the papers and the discussion given in a symposium held in Boston on February 9-10, 1952 under the auspices of the Boston Psychoanalytic Society and Institute. This is the first of a monograph series and was edited by Dr. Felix Deutsch. The symposium arose in answer to questions which had been raised concerning the status of the psychosomatic concept within the framework of Freudian psychoanalysis. Five areas were covered including genetic and dynamic determinants, current trends and hypothesis in research, the problem of specificity,

the genesis of symptoms in infancy and problems of therapy.

It was agreed that psychoanalysis or a therapy based on psychoanalytic principles seems to be the treatment of choice for psychosomatic disorders. Analytic investigators are now turning their attention to basic physiologic and pathologic phenomenon as well as to motor-sensory behavior patterns during the analytic session. O. E.

BIOCHEMICAL PREPARATIONS. VOL. 3. Edited by ESMOND E. SNELL, University of Texas. Pp. 128; 2 ills., New York: John Wiley & Sons, 1953. Price, $3.50.

THIS volume, like the others of the series, is a valuable supplement to the literature of biochemical methodology. Workers in the fields of carbohydrate, protein and amino acid metabolism should find it especially convenient (all except two of the twenty-four preparations could be classified as of use in one of these fields). Enzyme systems are utilized in the synthesis of six compounds and details are given for the isolation of two crystalline enzymes (ribonuclease and muscle phosphorylase). In keeping with newer techniques, ion exchange resins are used to purify several of the final products. Although in a few instances one might wish for more precise directions, for example, temperature permissible at which to concentrate under reduced pressure, (pp. 98 and 106), as a whole the precedures given are clear and easily followed. R. B.

HYPERTENSIVE DISEASES. CAUSES AND CONTROL. BY HENRY A. SCHROEDER, M.D., F.A.C.P., Associate Professor of Medicine and Director, Hypertension Division, Department of Internal Medicine, Washington University School of Medicine. Pp. 610; 164 ill; 3 colored plates. Philadelphia: Lea & Febiger, 1953. Price, $10.00.

THIS book is an extremely provocative one, as the author has intended it to be. It presents what he has learned and what he thinks about arterial hypertension, and leads up to the presentation of what he labels a specific form of therapy, the combination of hexamethonium and l-hydrazinophthalazine (Hyphex), administered according to a carefully delineated scheme. Much more attention is paid to etiology and mechanisms than to the secondary effects of hypertension since the latter are of little importance in the prevention and control by specific measures. Excellent chapters written by other authorities have been included (psychosomatic factors, the role of compounds of nitrogen, hormonal factors, and a discussion of pheochromocytomas), and these add much to the elaboration of the author's total concept of pathogenesis, as well as to the value of the volume in a didactic sense. The results which Dr. Schroeder has obtained with Hyphex treatment in severe hypertensive disease are indeed impressive and offer support for his use of the term "specific" with respect to this therapy. However, the volume must be accepted as a progress report (the author agrees to this) since there is an ominous aspect related to the increasing frequency with which L.E. cells and other manifestations of the collagen diseases are being recognized in association with l-hydrazinophthalazine administration. T. D.

MODERN TRENDS IN DIAGNOSTIC RADIOLOGY. SECOND SERIES. Edited by J. W. MCLAREN, M.R.C.P., F.F.R., Radiologist, St. Thomas's Hospital, London. Pp. 413; 359 ills. New York: Paul B. Hoeber, Inc., 1953. Price, $18.00.

THE original volume with this title and under the same editorial auspices appeared five years ago and covered largely different aspects of diagnostic radiology than those which receive attention in the present work. The present pre-eminence of Swedish radiology in Europe is illustrated by the fact that of the authors of 24 chapters, 11 are Swedish. The reader is provided with an excellent survey of the results that can be expected of modern diagnostic radiology with the application of the thoroughness and technical perfection which are particularly characteristic of the Swedish approach.

There are brief chapters on some technical advances including an intelligent and documented plea for much greater attention to the hazards of radiation exposure in diagnostic clinical radiology. Of particular interest are the chapters by Swedish radiologists on angiocardiography, a field in which the technical excellence of their work is particularly outstanding. Some examples are presented of the remarkable work of Wegelius in the angiocardiographic study of heart dynamics by securing roentgenograms simultaneously in two planes at right angles at the rate of 10 to 12 pairs per second. The technique of selective angiocardiography, with injection of the opaque contrast material via a catheter in the pulmonary artery or right ventricle, is also illustrated.

The work of French which has brought some order to the chaos of the so-called "abnormal small bowel pattern" is outlined. Flocculation of barium in the jejunum is usually due to mucus which may be secreted in excessive amounts in some pathologic states, notably sprue and celiac disease. Most patients with so-called abnormal small bowel pattern will show physiologic patterns when re-examined with the nonflocculating barium preparations which are now available.

The other chapters cover specialized aspects of diagnostic radiology in which recent advances have been made. H. S.

PERIODONTIA. BY HENRY M. GOLDMAN, D.M.D., Director of the Riesman Dental Clinic, Beth Israel Hospital, Boston, Massachusetts; Post-Graduate Faculty, School of Dentistry, University of Pennsylvania; Lecturer in Dentistry, Columbia University. 3rd ed. Pp. 790; 525 ills., 12 in color. St. Louis: C. V. Mosby Co., 1953. Price, $16.00.

THIS is an excellent textbook dealing with diseases of the peridental structures. There are twenty-nine chapters and the reader will find difficulty in arriving at a conclusion as to which chapter is the most outstanding.

The author stresses the importance of a clear understanding of the anatomy, histology, and physiology of the periodontium before discussing the various pathological changes that take place in these structures; and the therapy that may be instituted to improve the oral health of patients afflicted with diseases of the soft tissues and investing structures of the teeth.

It is by far the best text on the subject this reviewer has had the pleasure of reading and recommending as belonging in the office library of the practicing dentist. J. C.

DIURETIC THERAPY. BY ALFRED VOGL, M.D., Assistant Professor of Clinical Medicine, New York University College of Medicine. Pp. 248; 5 ills. Baltimore: Williams & Wilkins Co., 1953. Price, $5.00.

IT was the author of this book who, more than 30 years ago, discovered the diuretic effect of organic mercurial compounds by a process of serendipity. His interest in the subject of diuresis has continued through the intervening years, and he has provided for us in this volume a very concise and entirely adequate summary of the subject. Few physicians have had the opportunity to keep up with the large volume of literature that has appeared in recent years, particularly in relation to the whole subject of electrolyte metabolism, but herein it is given to them in a very readable and practical form. If Dr. Vogl's contribution is as widely read as it deserves to be, it should do much to reduce the haphazard misuse of these potent agents which is so prevalent in medical practice today.

T. D.

FRONTAL LOBES AND SCHIZOPHRENIA. Edited by MILTON GREENBLATT, M.D., and HARRY C. SOLOMON, M.D. Pp. 425; 35 ills. New York: Springer Publishing Co., 1953. Price, $12.50.

THIS book presents one of the most comprehensive studies of a surgical approach to chronic schizophrenia yet made. The work was carried out by a clinical and research team at the Boston Psychopathic Hospital. It records the results of 116 patients treated with lobotomy and surveyed by the fields of psychiatry, sociology, psychology, physiology and pathology. It is believed the benefits are derived from reducing through surgical means cells and circuits in the frontal lobe. Impulse energy and temporal delay are decreased. As a result (1) the patient loses drive, force, energy. (2) He is less affected by past experience. (3) He is less able to elaborate experiences and less able to sustain experiences. As a practical result of these losses there is a reduction in emotional tension, anxiety, fear, worry, hostility. There is a wealth of detailed observation and resulting conclusion in this book. It is a valuable survey of a surgical approach to this most important chronic mental illness which occupies so many hospital beds yearly.

O. E.

NEW BOOKS

Doctor at Sea. BY RICHARD GORDON. Pp. 191. New York: Harcourt, Brace and Co., 1954. Price, $3.00.

HAVING read and tremendously enjoyed the first book by Doctor Gordon, "Doctor in the House," the reviewer promptly read this new contribution of a physician with a superb sense of humor and a charming style, and found it very delightful. If you are a physician and have ever been aboard a ship, you must read "Doctor at Sea." R. K.

Add Life to Your Years. BY ERNST BOAS, M.D. Pp. 278. New York: The McBride Co., 1954. Price, $3.75.

THIS book is written for laymen. The author brings to his task a long-standing interest in geriatrics and long experience in medical writ-

ing. Laymen will find here much valuable advice to help them to add life to their years.
R. K.

Early Phases of Personality Development: A Non-Normative Study of Infant Behavior. By Sibylle Escalona, Mary Leitch and others. Pp. 72. New York: Child Development Publications, 1953. Price, not given.

A concise and reliable study on infant behavior carried out by adherents of the Freudian psychoanalytic school of thought. Informative, readable and recommended. O. E.

Science and Man's Behavior. By Trigant Burrow, M.D., Ph.D. Pp. 564; 26 ills. New York: Philosophical Library, 1953. Price, $6.00.

This is a book setting forth the philosophy and treatment approach of a physician who early in the twentieth century took an interest in the approach of Dr. Carl Jung of Zurich to the neuroses of man. The book is edited by a colleague of the author who survived him and it stresses the impact of society upon an individual and ignores to a large degree what there is within the individual to be affected by society.

The group treatment approach is stressed rather than individual therapy. The style is philosophical, detached and verbose and not of too much help to the clinician in every day problems.
O. E.

The Allergic Patient and His World. By Florence Eastty Sammis, M.D., Asst. Attending Physician in Allergy, Nassau Hospital, Mineola, N. Y. Pp. 156; 12 ills. Springfield, Ill.: Charles C Thomas, 1953. Price, $4.75.

The success of treatment in allergic patients depends in no small degree upon the intelligent cooperation of the patient. This little manual for the patient offers much practical information in helping him to avoid his hidden enemies.
R. K.

Psychology in the Nursery School. By Nelly Wolffheim. Pp. 144. New York: Philosophical Library, 1953. Price, $3.75.

This is a small and readable book by a school principal who discusses certain problems in the rearing of children as they are seen and dealt with in the psychoanalytically oriented Nursery School. There are seven chapters, three of them devoted to the philosophy of and orientation of the nursery. Such subjects as "Effects on Community Life of the Relationships between Brothers and Sisters," "Play and Occupation in the Nursery School," are discussed. This book can be heartily recommended to parents and teachers as a good basic orientation work on the early emotional development of the child. O. E.

It's Not All in Your Mind. By H. J. Berglund, M.D., and H. L. Nichols, Jr. Pp. 343. Greenwich, Conn.: North Castle Books, 1953. Price, $3.95.

This book, written for the layman, seeks to correct the overemphasis by some psychiatrists on the psychic factor in the production of disease. The authors pay particular attention to a field in which some of the more glaring errors have been committed, the field of allergy, and adequately justify the title of the book. R. K.

First Report of Expert Committee on Leprosy. WHO Technical Report Series No. 71. Pp. 28. Geneva: World Health Organization, 1953. (New York: Columbia University Press, U. S. Agents). Price, $.20.

Rat Quality. A Consideration of Heredity, Diet and Disease. Proceedings of the Symposium held at Columbia University, College of Physicians and Surgeons, New York, New York, January 31, 1952. By W. E. Heston, G. E. Jay, Jr., H. Kaunitz, H. P. Morris, J. B. Nelson, S. M. Poiley, C. A. Slanetz, Lois M. Zucker and T. F. Zucker. Pp. 138; 24 ills. New York: National Vitamin Foundation, 1953. Price, $2.50.

Arbeit und Gesundheit. No. 49. Zur Genese des Diabetes Mellitus und des Bronchialasthmas. Edited by Prof. Dr. M. Bauer. Pp. 113; 5 ills. Stuttgart: Georg Thieme Verlag, 1953. Price, DM 9.60.

Arbeit und Gesundheit. No. 50. Die entschädigungspflichtigen Berufskrankheiten. Edited by Prof. Dr. M. Bauer. Pp. 176. Stuttgart: Georg Thieme Verlag, 1953. Price, DM 9.60.

These paper-bound bulletins are No. 49 and No. 50 of a series published under the editorship of Dr. M. Bauer for the Ministry of Labor of the West German Government. No. 49 consists of nine papers by various authors concerning the etiology of diabetes and of asthma and their possible relation to occupation (the conclusions are overwhelmingly in the negative). No. 50 presents discussions, directives and minutes of meetings dealing with the various aspects of the occupational diseases subject to compensation. Their prime purpose is to acquaint German physicians with current views and usages in this field. Those interested in industrial medicine, who are able to read German, will find these publications highly instructive. R. K.

An Rh-Hr Syllabus. The Types and Their Applications. By Alexander S. Wiener, M.D. Pp. 82; 8 ills. New York: Grune & Stratton, Inc., 1954. Price, $3.75.

This small volume presents an up-to-date summary of the complex subject of Rh-Hr types. Chapters deal with fundamentals of serology, Rh antibodies, serology and genetics of the Rh-Hr types, erythroblastosis fetalis, blood transfusion, autosensitization, anthropologic aspects, and medicolegal applications. Anyone interested in this evergrowing field will find this a clear and easily understandable introduction. C. Z.

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1. Moyer, J. H.; Miller, S. I., and Ford, R. V.: J.A.M.A. 152:1121 (July 18) 1953.
2. Moyer, J. H.; Snyder, H. B.; Johnson, I.; Mills, L. C., and Miller, S. I.: Am. J. M. Sc. 225:379 (April) 1953.

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1. Meller, R. L., and Resch, J. A.: *Bull. Univ. Minnesota Hosp.*, 20:78, Oct. 8, 1948.
2. Meller, R. L., and Resch, J. A.: *Postgrad. Med.*, 6:452, Dec., 1949.

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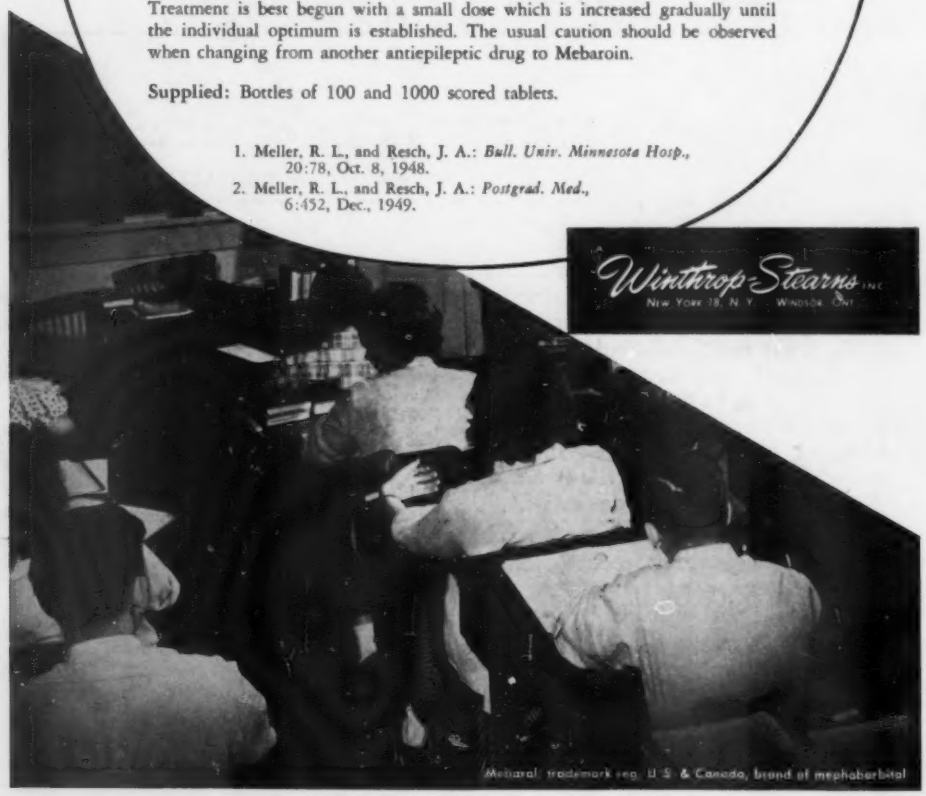

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